Chapter 12
Automated Peritoneal Dialysis

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Automated peritoneal dialysis (APD) is a term used to refer to all forms of peritoneal dialysis that employ a mechanized device to assist in the delivery and drainage of dialysate. Automated cyclers are used in intermittent peritoneal dialysis (IPD), nocturnal intermittent peritoneal dialysis (NIPD), continuous cyclic peritoneal dialysis (CCPD), tidal peritoneal dialysis (TPD), and continuous flow peritoneal dialysis (CFPD) [1–3]. In addition, some patients on continuous ambulatory peritoneal dialysis (CAPD) may receive one or more nocturnal exchanges with a night exchange device [4].

Automated PD is a fast growing modality for renal replacement therapy. The growth of APD has been facilitated by the development of new smart machines and increasing physician knowledge and patient acceptance. These machines have easy-to-use interfaces and incorporate microchips and computer technology enabling choice of therapies, safety features, and modalities to optimize therapy. Individualized therapies can be delivered to meet the lifestyle needs of the patient while ensuring adequacy of dialysis and ultrafiltration. Automation has dealt with some of the limitations of CAPD, including ultrafiltration failure, complications of increased intra-abdominal pressure, treatment fatigue, and failure to achieve clearance goals, and to some extent with noncompliance. Furthermore, in the new millennium, APD is poised to deliver a dose range beyond conventional dialysis and has the potential to deliver biocompatible solutions with specific compositions to meet individual needs by online preparation or regeneration of dialysate [5].

There has been a steady increase in APD utilization over the years: in 1998, only 21% of global PD patients were on APD and this number has increased by 1–2% annually [6] to approximately 30% at the end of 2004 [7]. Peritoneal dialysis grew by 6% between 2003 and 2004, largely driven by a 10% increase in utilization of APD. Mexico, the United Kingdom, and Korea are countries with the highest utilization of peritoneal dialysis, wherein treatment with APD modalities accounted for 21%, 32%, and 5% patients, respectively, in 2004 [7]. The French peritoneal dialysis registry reported the use of APD increased from 23% in 1995 to 36% in 2005 [8].

In the United States, even though the prevalent patients on peritoneal dialysis increased to 25,825 in 2003, there has been an overall decrease in the utilization of peritoneal dialysis for incident patients (USRDS 2005 Annual Data Report) [9]. The number of new peritoneal dialysis patients peaked at 8,530 in 1995 and declined to 6,690 patients in 2003. Of these, 2,100 (31.3%) patients were started on CCPD. Fifty-six percent of prevalent PD patients were on APD [9]. An industry report evaluating dialysis trends in the United States looked at four large cohorts of patients initiating peritoneal dialysis in 2000–2003 and found that majority of patients selected APD as their modality with a trend towards greater utilization from 58% in 2000 to 64% in 2003 [10]. This aberrancy from the USRDS Data Report may be due to inaccuracies in reporting of PD modality and a number of patients being reported with unknown modality. A prior report from the same group found that the proportion of patients on APD was over 60% in all age groups except those above 80 years of age [11].

CCPD was the modality of choice for 26% for all incident end-stage renal disease patients of age from 0 to 19 years, per the 2005 USRDS Data Report [9]. The North American Pediatric Transplant Cooperative Study Registry reported that APD was the modality at initiation and as well as throughout peritoneal dialysis follow-up for almost 70% of incident pediatric dialysis patients between 1992 and 1998 [12].

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History of APD

The first peritoneal cycler was described by Fred Boen et al. in the early 1960s [13, 14]. This device used a sterile dialysate prepared in the hospital and delivered to the bedside in 40-L carboys. Therapy consisted of multiple 2-L exchanges delivered over a 10-h period. An automatic solenoid device controlled delivery of the dialysate into the peritoneal cavity. In 1966, Norman Lasker and co-workers [15] described an automated cycler that became the forerunner of modern cyclers. This gravity-based machine utilized 2-L bottles of dialysate and disposable tubing. A preset volume of dialysate was delivered to the patient and was drained after a prescribed dwell time. At the same time as Lasker, Tenckhoff et al. [16] designed an automated system that mixed dialysate concentrate with distilled water processed by a "miniature still." This system proved to be expensive, bulky, and time consuming to use, and was soon abandoned. After the development of reverse-osmosis water, Tenckhoff et al. [17] adapted the technology to develop a new cycler. This cycler used reverse-osmosis water and a proportioning system to mix treated water with dialysate concentrate. Large amounts of dialysate could be easily prepared at a relatively lower cost. Higher glucose concentrations were achieved by adding hypertonic glucose to the mixture.

Cyclers were initially used for intermittent peritoneal dialysis (IPD). IPD was popular between 1970 and 1976 because the simplicity of the procedure permitted patients to perform home dialysis with or without the help of a partner [18]. Patients on IPD also enjoyed relative freedom between treatments to carry out other activities. However, IPD fell out of favor by the late 1970s because of poor outcomes due to inadequate dialysis and malnutrition [19–21]. In 1976, Popovich and co-workers [22, 23] described the concept of equilibrium peritoneal dialysis, moving the focus away from cycler-dependent treatments. They proposed that fluid left in the abdominal cavity over 4 h would equilibrate with blood urea. Five exchanges of 2 L each and 2 L of ultrafiltration would be required for controlling uremia. This method came to be called continuous ambulatory peritoneal dialysis (CAPD) [23]. The real revolution for CAPD came with the development of collapsible plastic bags for dialysate [24].

Interest in APD was revived by Diaz-Buzo et al. [25] and by Price and Suki [26]. They described the procedure called continuous cyclic peritoneal dialysis (CCPD), which is a form of automated equilibrium peritoneal dialysis. Patients receive three or four exchanges automatically at night and an additional exchange that remains in the abdomen through the day. The catheter is capped during the day and the patient starts the nocturnal exchange by emptying the peritoneal cavity.

A dialysis procedure that combined intermittent and continuous-flow technology was introduced in the late 1960s and early 1970s to increase the efficiency of IPD. This technique was initially introduced as recirculating peritoneal dialysis [27] and was later revived by Twardowski in 1989 and renamed tidal peritoneal dialysis (TPD) [28]. During this procedure, after an initial fill volume is instilled into the abdominal cavity, only part of the dialysate is drained and replaced by fresh peritoneal dialysis fluid with each cycle. The hypothesis behind this procedure is that leaving a "sump volume" in the cavity would improve clearances, as there would be constant contact between the peritoneal membrane and dialysate.

Peritoneal Dialysis Solutions

The traditional peritoneal dialysis solutions used for APD are the same as used for CAPD. The solutions are available in three different dextrose concentrations (1.5%, 2.5%, and 4.25% dextrose). The dextrose concentrations used for shorter dwells are generally 1.5% or 2.5%, while for the long dwell the preferable concentration is 2.5% or 4.25% to prevent excessive fluid absorption. The composition of the standard peritoneal dialysis solution is provided in Table 12.1. A problem occasionally seen in APD modalities using short dwells (NIPD, TPD) is the development of hypernatremia due to sodium sieving [29–32].

Several in vitro and in vivo studies have demonstrated the unphysiologic nature of conventional dialysis solutions [33–35]. Lactate, the low pH, high glucose, and glucose degradation products are likely the major determinants of

Table 12.1 Composition of standard solutions for automated peritoneal dialysis

Dextrose (%)	1.5, 2.5, 4.25
Sodium (mEq/L)	132
Potassium (mEq/L)	0
Calcium (mEq/L)	2.5–3.5
Magnesium (mEq/L)	0.5–1.5
Lactate (mEq/L)	35–40

bioincompatibility. Experiments by Breborowicz suggest that the cytotoxicity of peritoneal dialysis solutions is most evident immediately after instillation of dialysate and gradually declines within minutes of the dwell [35]. This decline in cytotoxicity occurs due to the residual intraperitoneal fluid and a rapid equilibration process in the peritoneal cavity. Since the impact of fresh peritoneal dialysis solutions is maximum at the beginning of the dwell time, there has been concern that the larger volumes of solution and more frequent exchanges during APD would cause a more rapid deterioration of the peritoneal membrane when compared with CAPD [36]. Comparison of CAPD and CCPD in an in vitro system showed no short-term detrimental effects on biocompatibility parameters indicative for peritoneal host defense, mesothelial cell integrity, and peritoneal fibrosis [36]. On the other hand, ex vivo studies on peritoneal macrophages have shown impaired local phagocytic and opsonic capacity with shorter dwells [37, 38].

With glucose-based therapies, the incidence of negative ultrafiltration during the long dwell is high [39]. This therapeutic failure with glucose-based solutions increases the requirements for enhanced ultrafiltration in the cycler-based nocturnal component of the therapy, resulting in the use of higher glucose tonicities and consequently greater glucose exposure [40]. Icodextrin is an alternative osmotic agent, which provides sustained ultrafiltration during the long dwell and is low in glucose degradation products [41–44]. It has a high molecular weight, which results in a sustained colloid osmotic gradient. Icodextrin is absorbed from the peritoneal cavity at a much slower rate than dextrose and consequently provides superior ultrafiltration per gram of absorbed carbohydrate [43]. Reduction of carbohydrate absorption may help reduce the metabolic complications of peritoneal dialysis [45]. In a computer-generated three-pore model, Rippe and Levin predict that ultrafiltration will keep increasing with icodextrin even after a 15-h dwell [46]. Most clinical studies in APD patients have shown that ultrafiltration with icodextrin is around 168–270 mL [41–44]. However, Finkelstein et al. in a study comparing icodextrin and 4.25% dextrose in high and high average transporters showed mean ultrafiltration with icodextrin in APD patients to be >500 mL with a dwell period of 14–16 h. Between 33 and 38% of patients in this study had negative ultrafiltration with 4.25% dextrose and none after 2 weeks of randomization to icodextrin [40]. A recent study showed maximum ultrafiltration with icodextrin dialysis solution in APD patients is achieved at 10 h, beyond which, increasing the dwell time does not lead to any significant increase in ultrafiltration [47]. Overall ultrafiltration with icodextrin during the day exchange in APD appears to be less than in the night exchange on CAPD. An upright posture and physical activity produce greater intraperitoneal pressure, resulting in increased lymphatic reabsorption during a daytime dwell [48].

A benefit of increased ultrafiltration with icodextrin is an increase in small solute clearances and sodium removal [40–43, 49]. The increase in sodium removal has been demonstrated to improve control of fluid balance [43, 49, 50]. Impact of icodextrin on blood pressure control on APD patients needs to be studied in a systematic manner with only one of the current studies showing improvement in blood pressure control [50]. With improved ultrafiltration, it was initially feared that there would be a negative impact on residual kidney function. However, current studies suggest that the use of icodextrin could preserve urinary volume and clearances compared to conventional peritoneal dialysates [49, 51].

Another benefit of icodextrin is that it produces less glycation of protein and appears more biocompatible [52]. The European Automated Peritoneal Dialysis Outcomes Study (EAPOS) measured longitudinal membrane function (solute transport and ultrafiltration capacity) annually in a prospective but nonrandomized cohort of 177 functionally anuric patients. The whole cohort experienced an increase in solute transport and reduction in ultrafiltration capacity at 12 and 24 months. A subgroup analysis according to glucose exposure and icodextrin use at baseline found these changes were accelerated and more severe in patients using either 2.27 or 3.86% glucose. Icodextrin use in these circumstances was associated with less deterioration in membrane function [53].

The use of icodextrin may cause a decrease in serum sodium and chloride levels. There is a decline in serum α-amylase activity, which likely has no clinical significance. A skin rash and exfoliate dermatitis may develop with the use of icodextrin [43, 54].

An innovative development from the standpoint of APD has been the introduction of bicarbonate solutions. These solutions are packaged in dual chambered bags or potentially, in the future may be generated online. The dual-chambered bags separate calcium and magnesium from bicarbonate. These bags contain physiologic concentrations of bicarbonate and allow dialysate to be delivered at a physiological pH. Furthermore, the two chambers allow glucose to be sterilized at a very low pH, minimizing the generation of glucose degeneration products [55]. Currently marketed are peritoneal dialysis solutions contain 25 mmol/L of bicarbonate with either 10 or 15 mmol/L of lactate, allowing for flexibility in control of acidosis. An alternative solution contains only bicarbonate (34 mmol/L) as a buffer (Table 12.2). On-line production of dialysate was first described by Tenckhoff [16, 17]. More recently, a machine used for online production of a replacement fluid for hemofiltration was adapted to produce peritoneal dialysate [56]. The machine utilizes reverse osmosis water and a proportioning system to mix a standard acid concentrate with a bicarbonate bath. Such systems could potentially decrease costs associated with high-volume therapies and offer customization of dialysate to meet the needs of an individual patient.

Table 12.2 Composition of bicarbonate-based peritoneal dialysis solutions

	Bic/Lac 35	Bic/Lac 40	Bicarb 34
Sodium (mEq/L)	132	132	134
Calcium (mEq/L)	1.75	1.25	1.75
Magnesium (mEq/L)	0.25	0.25	0.5
Chloride (mEq/L)	101	95	104
Bicarbonate (mMol/L)	25	25	34
Lactate (mMol/L)	10	15	0
Dextrose %	1.5, 2.5, 4.25	1.5, 2.5, 4.25	1.5, 2.5, 4.25
Ph	7.4	7.4	7.0–7.6
pCO_2 (mm Hg)	48	48	60

Bicarbonate-based peritoneal dialysis solutions are more physiological, and are especially indicated for children in whom hepatic conversion of the buffer lactate to bicarbonate is rate-limited, in patients requiring dialysis for acute renal failure, or those with hepatic dysfunction [57]. These solutions are associated with lesser infusion pain and improvement in biocompatibility parameters including enhanced phagocytic activity of peritoneal macrophages, reduced constitutive inflammatory stimulation, reduced advanced glycosylation end products accumulation, and better preservation of the mesothelial cell integrity [58, 59]. Children dialyzed with conventional peritoneal dialysis solutions may need additional bicarbonate to correct acidosis; a switch to bicarbonate [59] or bicarbonate/lactate solutions improves acid-base balance and may even cause alkalosis [60]. Subtle changes in solute transport may be noted on peritoneal equilibration tests during bicarbonate dialysis with a less steep creatinine equilibration curve suggesting reduced peritoneal vasodilation [59].

Amino acid–based peritoneal dialysis solutions may be an option for the malnourished patient on APD. A 1.1% amino acid solution provides ultrafiltration roughly equivalent to a 1.36% dextrose solution [61]. Studies have established the benefit of amino acid peritoneal dialysis solutions in continuous ambulatory peritoneal dialysis [62, 63]. For adequate absorption on APD, the amino acid solutions would have to be used for the long dwell. An option to achieve adequate ultrafiltration would be to combine an amino acid solution with glucose or a glucose polymer [64]. In a crossover study, combined administration of dextrose and amino acid in the peritoneal dialysate improved protein anabolism in APD patients [65].

Peritoneal Dialysis Cyclers

The use of sophisticated software and hardware has made the present generation of cyclers safe, reliable, and easy to use while allowing these devices to become compact and portable. Most cyclers offer built-in programs with options for all the varied modalities of automated peritoneal dialysis, including CCPD, classical IPD, NIPD, TPD, and CFPD. These machines are programmable for dialysis modality, inflow volume, fill, dwell and drain times per cycle, last bag fill options, and additional daytime automated exchanges. Most cyclers automatically monitor infusion and drainage rates. They increase treatment efficacy by eliminating lag-time between exchanges after a predetermined volume has drained and the drain has slowed below a certain threshold. The cyclers are equipped with on screen displays, which provide instructional steps, including troubleshooting alarms.

Recent sophistications include flash memory cards and modems. The memory card serves two functions: To program the patient's prescription into the cycler and to collect information about treatments. The card is programmed at the center with the desired prescription and then uploaded into the cycler. In some machines, the card can contain information about several prescriptions and the patient could choose the most appropriate for a particular session. The card also records details of each treatment, including ultrafiltration, total volume, fill volume, drain time, cycle time, and any alarms, eliminating the need for paper records. Information regarding compliance such as shortened or missed treatments, changes in fill volumes, and bypassed therapy phases are recorded. This information is easily converted by software into easy-to-interpret charts and graphs allowing for quick identification of problems. The data card can be brought by the patient for their visit or be uploaded to the center through a modem.

Cyclers are equipped with easy-to-install disposable tubings. The tubing manifold has several prongs for spiking dialysate bags and a single prong leading to the patient. Some cyclers provide for automatic connection and bag identification using laser bar-readers. The use of large-volume dialysate bags has reduced the costs of treatment, as well as the number of required connections. The dialysate is moved from the dialysate bags to a reservoir bag and then instilled into the patient. After the designated dwell time is complete, the dialysate is either emptied into a bag or

drained directly. The movement of dialysate through the cycler and in and out of the patient is mediated by gravity, pump-driven systems, or a combination of the two. Fluid is preheated in the reservoir bag, which is placed on a heater cradle. The preheating of the fluid is done more for the patients' comfort rather than to prevent hypothermia. Integrated scales allow accurate delivery of the fill volume and measurement of drainage and ultrafiltration volumes. Cyclers with pediatric treatment options can deliver volumes as small as 50 mL with the option of 10-mL increments [66].

Ronco et al. [66, 67] predict that, in the future, cyclers will be capable of optimizing therapy and delivering appropriate solutions. Machines will be equipped with sensors capable of measuring intraperitoneal pressure in addition to flow sensors. Segmental bioimpedance measurements may be incorporated to measure intraperitoneal fill volumes and ultrafiltration during rapid APD therapy. These devices will allow for detection of catheter malfunction as well as allow the machine to tailor make the next dialysis exchange with regards to osmolality, dwell time, and cycle volume. A fine control of ultrafiltration could be achieved by altering sodium and glucose concentrations in the dialysate. These futuristic machines will monitor pO_2, pCO_2, and pH in the effluent to perfect on-line production of bicarbonate-based dialysate with intelligent feedback. Measurement of urea and creatinine in the spent dialysate will permit assessment of adequacy. Biosensors capable of detection of white blood cells will help with the early diagnosis of peritonitis.

Physiology of Solute and Fluid Transport

Physiological principles of solute and water transport are discussed extensively in Chapter 6. APD modalities introduce a biphasic profile for both clearances and ultrafiltration behavior by the use of short dwell exchanges during the night and a day dwell that may be much longer than the overnight dwell in CAPD.

Solute Transport

Solute transport across the peritoneal membrane is dependent on diffusion and convection.

Solute Transport by Diffusion

The diffusive transport of solutes is a function of the membrane transport characteristics, dialysate flow rate, peritoneal capillary blood flow rate, concentration gradient, and time allowed for transport [68].

The membrane transport characteristics can be assessed by a variety of clinical tests. The most commonly used technique to evaluate the peritoneal transport characteristic is to measure the dialysate to plasma solute concentration (D/P) for particular solutes during an exchange with conventional peritoneal fluid. This procedure has been standardized by Twardowski et al. [69, 70], and named the peritoneal equilibration test (PET). Patients are classified into four membrane categories: high, high average, low average, and low. Other measures of peritoneal transport are the mass transfer coefficients (MTC) and the peritoneal permeability analysis [71–73]. The MTC is the solute clearance rate that would be achieved across the peritoneum in the absence of both ultrafiltration and solute accumulation in the dialysate. Various numerical models have been described to calculate the MTC. The standard peritoneal permeability analysis (SPA) is a modification and extension of the PET: glucose1.36% dialysate is used, to which dextran 70 is added for the calculation of fluid kinetics. Mass transfer area coefficients (MTAC's) of low molecular weight solutes, clearances of proteins and the change in intraperitoneal volume (IPV) are assessed.

High or rapid transporters tend to equilibrate small solute concentrations between dialysate and blood early in a dwell. These patients also absorb glucose early in the dwell. Once the osmotic gradient has dissipated, ultrafiltration ceases, and the dialysate returns are reduced because of reabsorption of fluid. These patients are best served by short dwell treatments. On the other hand, patients with low transport rates achieve peak ultrafiltration late during the dwell, and D/P ratios increase almost linearly over a long dwell. These patients benefit from continuous regimens, as the total dialysis time is crucial for adequate clearances [74]. These principles are illustrated in Fig. 12.1 and recommended peritoneal dialysis modalities are suggested in Table 12.3.

Several factors affect the MTC; important from the APD standpoint are the position during dialysis and the dialysate exchange volume (V_{ip}). Using the same V_{ip}, the MTCs for urea and creatinine were increased 24% and 19% in one study [75], and 15% and 9%, respectively in another study [76] in the supine position when compared with the upright position. In the supine position, the dialysate layers throughout the entire abdominal cavity, while in the upright position dialysate pools in the subumbilical region of the abdomen. The increase in the MTC is caused by increased contact of dialysate with

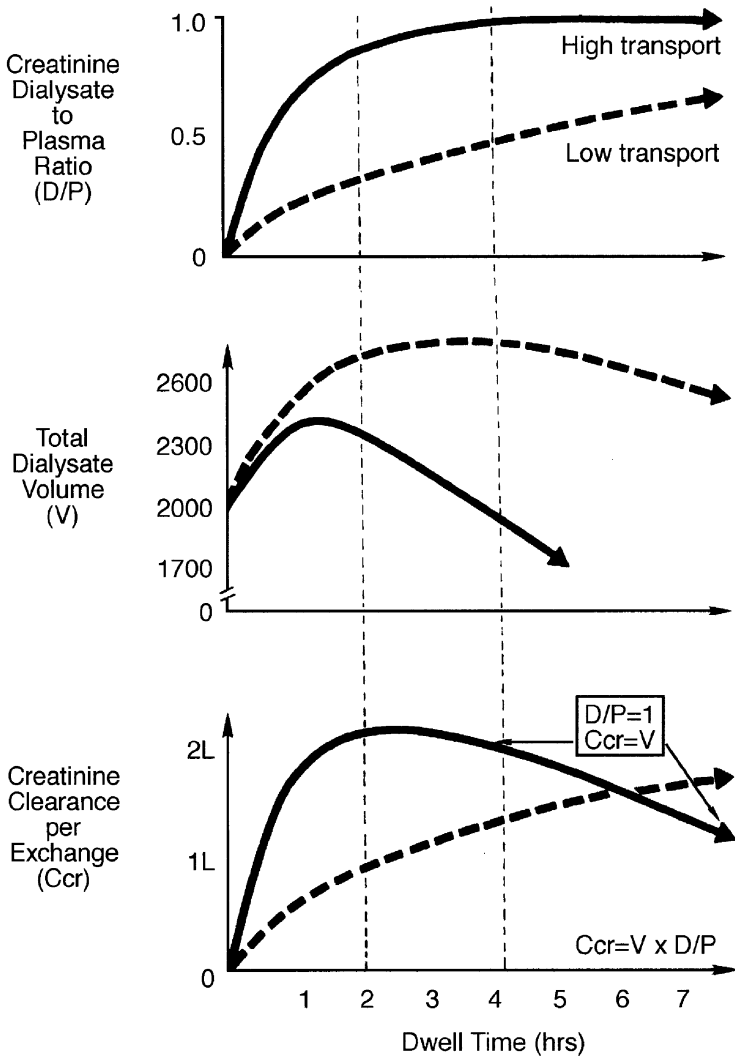

Fig. 12.1 Idealized curves of creatinine and water transport during exchange with 2 L of 2.5% glucose dialysis solution in patients with extremely low and high peritoneal transport characteristics. Upper panel shows dialysate to plasma ratio (D/P); middle panel shows total dialysate volume (V), which is the sum of infusion volume and ultrafiltration; lower panel shows creatinine clearance per exchange (C_{cr}). The curves in the lower panel are derived from those of the upper and middle panels. ——, high peritoneal transport; - - - -, low peritoneal transport. From Ref. [74] with permission

the peritoneal membrane. Additionally, in the supine position, dialysate is more accessible to the peritoneal membrane around the liver [76]. The peritoneal membrane around the liver accounts for up to 45% of the total MTC for the entire peritoneal cavity [77]. Portal blood flow also increases in the supine position [78].

An increase in the V_{ip} increases solute clearances by an increased plasma to dialysate concentration gradient and/or to an increased effective peritoneal area [79]. Schoenfeld et al. [80] observed a strong linear relationship between the peritoneal transport constant and V_{ip}. These correlations occurred over a range of 1–3.8 L of V_{ip}. Keshaviah et al. [81] found that the V_{ip} associated with peak MTC increased with increasing body surface area, and a fill volume of approximately 1,500 mL/m^2 body surface area provides a maximal MTC. Higher fill volumes do not improve dialysis efficiency further. A study using computerized tomography to assess the effect of increased dialysate volume from 2 to 3 L found an 18% increase in peritoneal surface area in contact with dialysate and consequently enhanced the MTC. In spite of a 50% increase in fill volume, the larger volume does not make contact with the entire peritoneal dialysis surface area [79]. Increasing the V_{ip} is a more effective means of increasing solute clearances than more frequent exchanges with lower V_{ip}. This practice also reduces dialysate transit time, or the non-dialytic period, and improves clearances. Increases in $V_{ip,}$ however, will increase the intra-abdominal pressure which may decrease ultrafiltration.

Table 12.3 Preferred peritoneal dialysis modality based on solute transport

Solute transport	Preferred modality
High	NIPD, CCPD, TPD
High-average	CAPD, CCPD, CCPD + CAPD, TPD + CAPD
Low-average	CAPD, CCPD, CAPD+ CCPD
Low	CAPD, HD

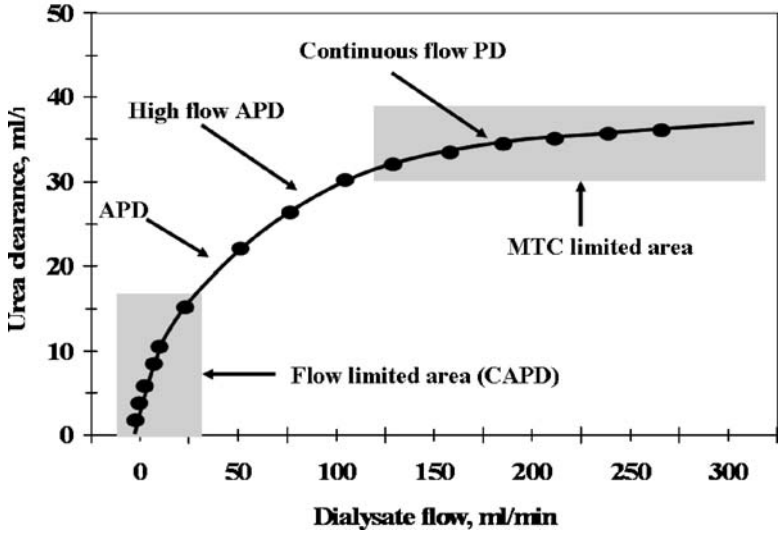

Fig. 12.2 Relationship between urea clearance in peritoneal dialysis and dialysate flow rate. From Ref. [82] with permission

The impact of dialysate flow on urea clearance is demonstrated in Fig. 12.2 [82]. The initial portion of the curve corresponds with the dialysate flow rates typical of CAPD (three to five exchanges per day). In this region of the curve, there is a steep correlation between urea clearance and dialysate flow rates. CAPD is, therefore, dialysate flow limited, and improved clearances may be achieved by increasing the number and/or the volume of exchanges. The second region of this curve is typical for APD. This region is affected by both the dialysate flow rate and MTC. As dialysate flow is increased in automated regimens, the dwell times become shorter, and an increasing proportion of exchange time is occupied by the inflow and drainage times [82, 83]. Although clearances may be improved by increasing dialysate flow, a point of diminished return will eventually be reached. Continuous flow peritoneal dialysis and tidal peritoneal dialysis try to address this issue by increasing contact time between dialysate and the peritoneal membrane. In tidal peritoneal dialysis, only part of the fluid is drained and replaced during an exchange [28]. Continuous flow peritoneal dialysis [84] through two catheters or a double-lumen catheter secures full contact of the dialysate with the peritoneal membrane, but at high flow rates, fluid channeling may restrict mixing [85].

The above illustrates that higher urea clearances can be achieved by increasing dialysate flow rates. Creatinine, urates, phosphates, and middle molecules equilibrate at a slower rate and hence clearances are lower than for urea. These kinetic characteristics of APD create adequacy discrepancies between Kt/V_{urea} and creatinine clearance [86]. The absorption of glucose is characterized by an exponential decay, shorter dwells reduce absorption of dextrose and improve ultrafiltration. Adequate ultrafiltration may be obtained while using low glucose concentrations in conjunction with high dialysate flow rates [86].

Solute Transport by Convection

Solutes accompany the bulk flow of water from the peritoneal capillary blood into the peritoneal membrane by convection (solute drag). For high-molecular-weight solutes, the convective transport is more important than the diffusive one. The magnitude of convective transport is determined by the ultrafiltration rate for the peritoneal membrane, the average solute concentrations within the membrane [87] and the sieving coefficient (S, describing the fraction of solute that passes through the membrane with water flow: $0 \leq S \leq 1$) [29, 30].

Although the sieving effect influences each solute, the important clinical consequence of sieving is related to sodium. The ultrafiltrate is usually low in sodium. Thus, dialysate sodium concentration is initially reduced in the dialysate and tends to increase late in the dwell due to diffusion of sodium into the dialysate and diminished ultrafiltration in longer dwells [29–32, 69]. During APD with shorter dwells, the net electrolyte removal per liter of ultrafiltrate remains far below the extracellular fluid concentration and severe hypernatremia and hyperosmolality may develop [88]. Ortega et al. [89] compared sodium removal in 36 patients undergoing CAPD and APD. Average peritoneal sodium removal was 195 mmol/day in CAPD and 87 mmol/day in APD, a difference attributed to lower ultrafiltration provided by APD. Part of the differences in ultrafiltration and sodium removal between CAPD and APD may be due to overfill of dialysis bags. In CAPD, the overfill is drained into the same bag submitted for laboratory analysis leading to an overestimation of ultrafiltration and sodium removal. The cycler patients use a single, smaller-volume flush that is discarded at the time of set-up and the cyclers provide fairly accurate estimates of instilled and drain volumes [90]. In a

larger study, Rodríguez-Carmona and Fontán [91] reported that total sodium removal was 210 mmol/day for CAPD and 91 mmol/day for APD, after taking into consideration overfill. Sodium removal of less than 100 mmol/day was present in 7.1% of CAPD patients and 56.4% patients on APD in their study. The use of icodextrin, supplementary diurnal exchanges, and longer nocturnal dwell times improves sodium removal in APD. An alternative is to reduce the dialysate sodium concentration. Since commercially available dialysis solutions do not offer this option, one may mix a 5% glucose solution (D5W) in appropriate proportions to achieve lower dialysate sodium concentrations [74].

Fluid Transport

Ultrafiltration

The net ultrafiltration is determined by the difference between the transcapillary ultrafiltration (TCUF) and absorption of fluid from the peritoneal cavity. The latter consists of transcapillary back-filtration and fluid uptake into the lymphatic system. The transcapillary ultrafiltration gradient is dependent on the hydraulic permeability of the peritoneum, its effective surface area, and the hydrostatic and the osmotic (colloid and crystalloid) pressure gradients [92, 93].

The transperitoneal crystalloid osmotic gradient is established by dextrose. The dissipation of dialysate/plasma glucose gradient during peritoneal dialysis is nonlinear, with a rapid initial decline followed by a slow decrement. The shorter nighttime cycles in APD take advantage of the high initial ultrafiltration rate. Further, the shorter the dwell time, the more preserved is the osmotic gradient and lower the difference for ultrafiltration across different membrane transport types. On the other hand, during the long daytime dwell, there is dissipation of the osmotic gradient and hence loss of the stimulus for ultrafiltration. High and high-average transporters are at most risk for negative ultrafiltration. This is best addressed by shortening the day dwell, or the use of higher dialysate tonicities or icodextrin [94].

The hydrostatic pressure in the peritoneal capillaries may be assumed to be 17 mm Hg [95]. The opposing hydrostatic pressure in the peritoneal cavity (intraperitoneal pressure) varies depending on the V_{ip} and posture and activities and may range from 5 mm Hg in the supine position, to over 20 mm Hg while standing and over 200 mm Hg with certain activities [96, 97]. In the supine position, the intraperitoneal pressure (IPP) is the least. However, with the use of larger volumes to augment clearances, the IPP will rise and impact transcapillary ultrafiltration and more so increase back filtration and lymphatic absorption [98].

Lymphatic Absorption

Along with ultrafiltration, there is a constant absorption of fluid from the peritoneal cavity. Fluid and solutes are reabsorbed directly by the lymphatics and also by a process of back-filtration into the peritoneal interstitium [99–101]. Fluid and solutes entering the peritoneal interstitium are taken up by the local lymphatics and capillaries. The IPP is a major determinant of egress of fluid from the abdominal cavity into the tissues lining the peritoneal membrane [100–102] and consequently the IPP influences the lymphatic absorption rate [98].

The subdiaphragmatic lymphatics account for the major portion of the fluid reabsorbed by lymphatics [99]. Lymphatic absorption is dependent on diaphragmatic movements and contact of fluid with the diaphragm. There is an increased contact of fluid with the subdiaphragm in the supine position and enhanced fluid absorption [103, 104]. Thus, in supine APD, two conflicting variables affect lymphatic fluid reabsorption: one, the lower IPP and two, the increased contact of fluid with the subdiaphragm.

Relationship Between Intraperitoneal Volume and IPP

Physical characteristics such as gender, body size, abdominal muscle tone, duration on peritoneal dialysis, and infused dialysate volume influence IPP. The empty peritoneal cavity has an IPP of 0.5–2.2 cm H_2O. The IPP rises in direct proportion to the amount of fluid infused into the abdominal cavity. Studies from APD show increases in IPP from 3.76 to 6.11 cm H_2O per liter of intraperitoneal fluid in the semi recumbent position [105–107]. Durand et al. demonstrated a rise in the IPP of 2 cm H_2O per liter of infused dialysate in the supine position [108]. A study measuring IPP in CAPD patients in the supine position found a strong inverse relationship between the dialysate volume/BSA ratio and IPP. This inverse relationship means that for any given fill volume, patients with smaller body size have a higher IPP than do patients with larger body size [109].

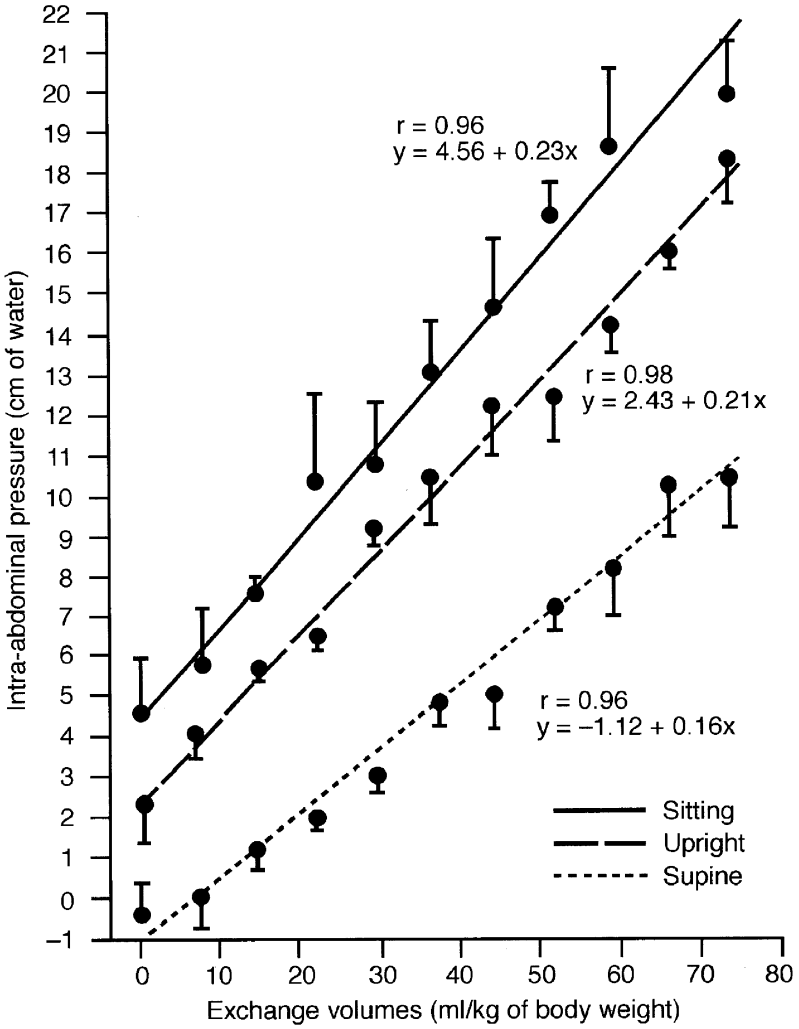

Fig. 12.3 Comparative effect of dialysate volume and patient position on intra-abdominal pressure. From Ref. [97] with permission

The relationship between IPP and V_{ip} is maintained regardless of the patient's position, but the slope of the curve does shift with changes in position. For any intraperitoneal volume, IPP is minimized by assuming the supine position; sitting leads to the highest pressures, and standing results in intraperitoneal pressures between those seen with sitting and lying down (Fig. 12.3) [96, 97, 107].

An increase in the IPP can cause a decrease in the net ultrafiltration [110]. A change in posture from supine to upright was associated in one study with a small increase in lymphatic absorption (+8%) and a decrease in transcapillary ultrafiltration (–5%), largely attributable to change in the IPP [104]. In another study, an increase in the IPP by 1 cm of water was found to cause a decrease in ultrafiltration of 74 mL at 2 h [111].

Dialysate Fill and Drain Profiles

It is generally known that dialysate fill rate is a function of fill height and patient position. The lower IPP in the supine position facilitates a higher fill rate for dialysate than in the upright position. Increasing drain height can also shorten the drain rates. Larger-bore catheters do not provide better fill rates, but may decrease the drain time [75].

The characteristic drain profile shows a bimodal pattern with high drain rate (>200 mL/min) for the initial 5–7 min, during which time over 80% of the dialysate is drained; followed by a very abrupt transition to a very slow drain rate (<50 mL/min) (Fig. 12.4) [75, 112]. A variable intraperitoneal volume is left at the breakpoint ranging from 0 to 1,200 mL, with an average of 500 mL [113]. This abrupt transition between outflow rates may happen due to bowelloops

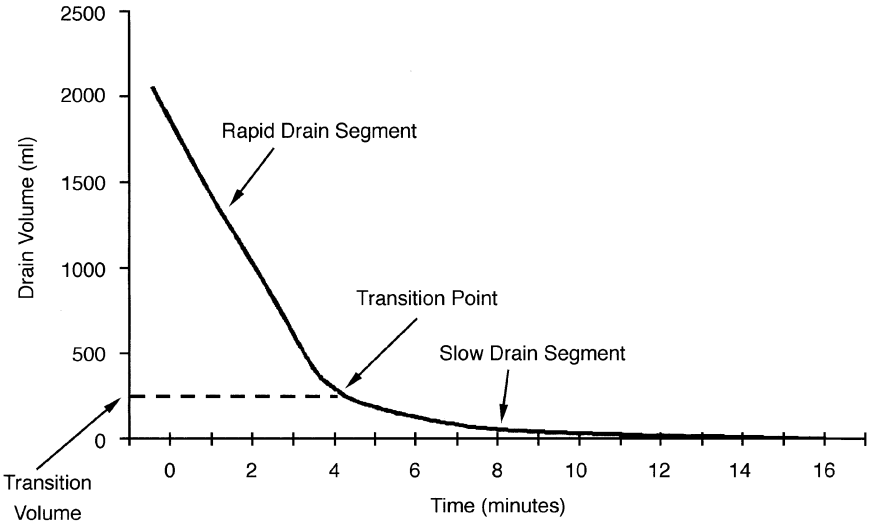

Fig. 12.4 Representative dialysate drain profile. From Ref. [75] with permission

collapsing on the catheter as the transition volume is approached, causing a significant reduction in outflow [75]. An alternative explanation is that the breakpoint may be due to a sudden drop in the conductance of the hydraulic system – when a critical intraperitoneal volume is reached, outflow from the abdomen becomes restricted [112]. The IPP is the force behind the drainage phases and at breakpoint, an equilibration between the V_{ip} and the IPP is possibly reached.

From the above discussion it is clear that a majority of the drain time during each cycle in APD is spent removing a small percentage of the total dialysate. Tidal peritoneal dialysis, wherein a tidal volume is exchanged in each cycle, utilizes only the rapid drain segment and obtains maximal benefit of this mechanism. A further refinement is breakpoint APD that refers to a tidal PD characterized by a variable reserve volume determined by the breakpoint allowing for optimization of drainage times. The effects of optimizing drain cycles are discussed subsequently in this chapter.

Factors Influencing Selection of APD

APD is the fastest-growing modality of peritoneal dialysis worldwide. However, there is a high variance in the use of APD in different areas of the world. Medical limitations, physician education and biases, availability and cost of equipment and supplies, patient preferences, social reasons, and reimbursement concerns impact the selection of dialysis modality [114].

The choice of APD over CAPD should initially be based on the patient's preference. The increased convenience of these treatments makes them more suitable for patients who have work commitments during the day. APD is the modality of choice in children and adolescents. The main reasons for these are the following: peritoneal diffusion is higher in children [115], freedom from bag exchanges in the daytime, no need for venipunctures, and no major effect on the work schedule of their parents [116, 117]. Elderly patients and those with manual or visual impairments who are dependent on assistance from others opting for peritoneal dialysis are best treated by APD to prevent overwhelming their partners or helpers [117, 118]. Patients, especially children who develop psychosocial problems due to distortion of body image by a protruding abdomen, should also be treated by APD [116].

From a physiological standpoint, the choice of peritoneal dialysis modality is best guided by the nature of the peritoneal membrane transport characteristics. Optimum therapy is achieved by matching modality and dwell times to the transport type of the patient [70, 74] (Table 12.3). Patients with high peritoneal transport characteristics and minimal residual kidney function (RKF) are best treated with APD to maintain adequate ultrafiltration. APD may need to be considered as a modality for patients with ultrafiltration failure. Larger patients and those with declining RKF needing higher fill volumes to achieve adequacy are candidates for APD as they may be more comfortable with doing these exchanges while supine. APD is a viable option for patients with complications due to increased intra-abdominal pressure (hernias, dialysate leaks, hemorrhoids, uterine prolapse, and back pain) [6]. From our earlier discussion, IPP is much lower in the supine position for the same dialysate exchange volume. Tidal peritoneal dialysis is indicated for patients who have drain problems or patients with infusion pain or pain at the end of a drain. APD may be offered to patients feeling burnout from CAPD [67].

However, APD is not an option for all patients. Higher costs due to the need of a cycler, disposable tubing, and generally larger dialysis volumes serve as a deterrent. Some patients may not accept the prolonged restriction to bed for the duration of overnight cycles or the dependence on a machine. There is a potential for sleep disturbances by machine alarms [118]. Sodium sieving may lead to hypernatremia, increased thirst, and poor blood pressure control [88].

Different Regimens of APD

Classical Intermittent Peritoneal Dialysis

Intermittent peritoneal dialysis (IPD) is a term used for dialysis regimens wherein periods on dialysis alternate with those when the peritoneal cavity is dry [3]. During classical IPD the patient receives several short dwell exchanges over 12–24 h with a dialysis dose between 40 and 60 L, several times a week but usually not every day. Though the procedure can be performed manually, automated cyclers or systems with on-line generation of dialysate are more practical. Treatments may take place in-center or at home.

Classical IPD is no longer used as a modality of chronic renal replacement therapy because of poor clearances and high morbidity and mortality [19–21]. However, the procedure continues to be used in countries where there are few alternatives for dialysis [119]. IPD may serve as an alternative to hemodialysis in patients needing immediate dialysis after peritoneal catheter placement. Small-volume supine dialysis is recommended during this period of catheter break-in. Cheng et al. [120] reported a higher incidence of pericatheter leaks, especially among diabetics started on IPD during the break-in period. IPD may be used as a transient therapy for patients who have hernias or leaks or those who have recently undergone abdominal surgery [121]. Some leaks may spontaneously seal off with lower intra-abdominal pressures on supine IPD. Another area of application of IPD is refractory heart failure on maximal medical therapy. Several studies have documented the reduction in morbidity days, and improvement in functional status [122–124]. Peritoneal ultrafiltration has not been shown to improve survival in most studies [125].

Nocturnal Intermittent Peritoneal Dialysis

Nocturnal intermittent peritoneal dialysis (NIPD) is an intermittent dialysis regimen performed every night, and may be considered to be similar to CCPD with a dry day (Fig. 12.5) [3]. NIPD treatments are performed overnight on a cycler. The dialysis usually lasts between 8 and 12 h. Dialysate volumes of 8–12 L are typically used for therapy per night, though larger volumes of dialysate and extended dialysis may be required for some patients.

The dry days eliminate 10–20% of small solute clearances achieved in a patient who is an average transporter on nightly cycles plus a wet day [126, 127]. Treatment of patients with NIPD has a greater impact on the clearance of middle molecules. The clearance of middle molecules is a time-dependent process, and dry days reduce clearances by 50% [126–128].

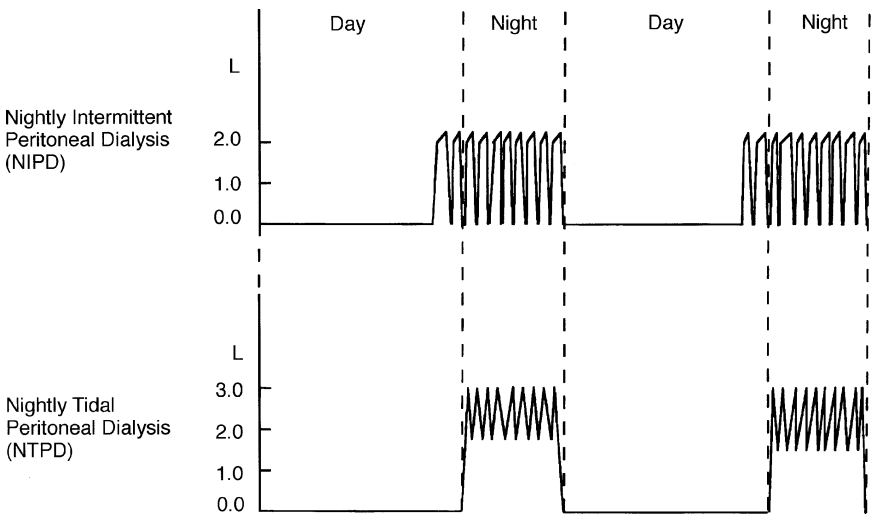

Fig. 12.5 Nightly peritoneal dialysis. Upper panel shows nightly intermittent peritoneal dialysis; lower panel shows nightly tidal peritoneal dialysis. From Ref. [3] with permission

NIPD may be an optimal modality for those with complications due to elevated intraperitoneal pressure, who are unwilling, or are not candidates for hemodialysis. Patients with high transport characteristics and those with type I ultrafiltration failure may also be treated with NIPD [74, 127]. Those patients with high levels of RKF may initially be treated with NIPD. This modality is not an option for subjects with large body surface area and those with average or below average transport characteristics with minimal or no RKF as adequacy parameters cannot be met [126]. NIPD does offer the psychosocial advantage of a better body image and lower glucose absorption leading to a better appetite. The costs of treatment run higher than with CAPD, and patients often do not accept the prolonged confinement to bed. Additionally, sodium sieving and the consequent low sodium in the ultrafiltrate may lead to hypernatremia, increased thirst, and worsening hypertension [88].

Continuous Cyclic Peritoneal Dialysis

Continuous cyclic peritoneal dialysis (CCPD) is a continuous automated peritoneal dialysis regimen [3] (Fig. 12.6). The technique is essentially a reversal of CAPD where the shorter exchanges are automatically provided at night while the longer exchanges are performed during the day. After the last nocturnal cycle the cycler is programmed to deliver a final exchange (last bag fill) of hypertonic dialysate or an alternative osmotic agent like icodextrin.

Small solute clearances are slightly lower in CCPD than in CAPD for the same dialysate flow [129, 130]. The total weekly clearances of middle molecules are the same as CAPD. The solute clearances may be improved by increasing the delivered intraperitoneal volume, increasing the number of nightly exchanges and duration on the cycler. A hybrid modality to increase adequacy and ultrafiltration is called PD Plus or CCPD + CAPD, wherein additional daytime exchanges are performed in addition to CCPD [131]. These daytime exchanges may be performed manually or by hooking back to the cycler.

This regimen is best suited for schoolchildren and employed patients who are frequently unable or unwilling to perform multiple daytime exchanges. Patients requiring assistance in performance of dialysis are better served by CCPD than CAPD. Connections and disconnections may be minimized to two, reducing burden on the provider. This is obviously an ideal choice for institutionalized patients.

Tidal Peritoneal Dialysis

Tidal peritoneal dialysis is a regimen combining intermittent and continuous-flow technology. The procedure attempts to increase efficiency by maintaining a reserve volume in the peritoneal cavity at all times, providing for uninterrupted solute clearance [28, 132]. In classical TPD, after an initial fill of the peritoneal cavity, only a portion of dialysate is drained and replaced by fresh dialysate (tidal volume) leaving the rest of the volume (reserve volume) in the peritoneal cavity (Fig. 12.5). Often the tidal volume is expressed as a percentage of the initial fill volume. For example with a 50% TPD with an initial 2L fill, subsequent tidal volumes would be 1L. Prediction of ultrafiltration is important to assure the reserve volume

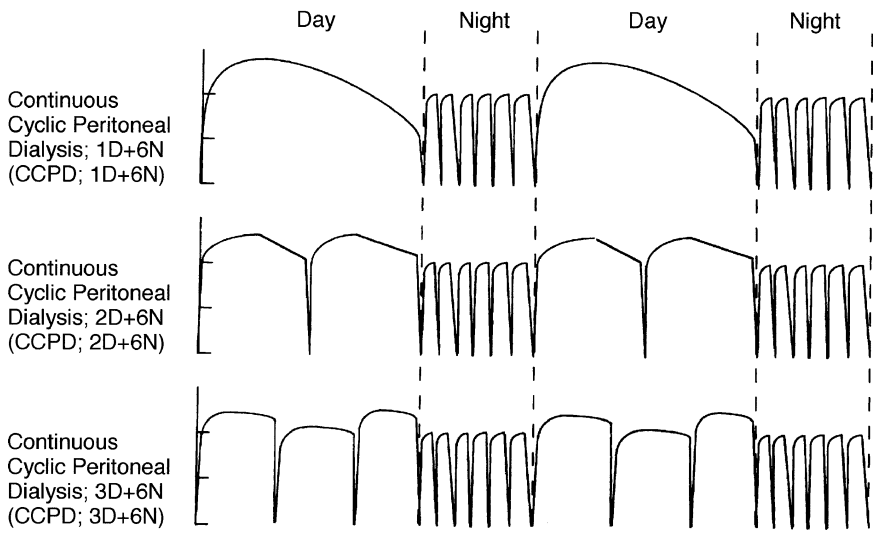

Fig. 12.6 Continuous cyclic peritoneal dialysis (CCPD). Upper panel shows standard CCPD with last bag fill; middle and lower panels show CCPD combined with additional daytime exchanges. From Ref. [3] with permission

remains unchanged. If ultrafiltration volumes are overestimated, the reserve volume would gradually be depleted. If ultrafiltration volumes are underestimated, the reserve volume will gradually increase leading to abdominal discomfort.

The initial studies comparing TPD and other APD modalities utilized much higher dialysate flow rates in TPD and found improved solute clearances. Among these studies was one by Flanigan et al. [132], which showed that utilizing 16 L of dialysate in TPD over 8 h provides equivalent clearances to 9.5 L for CCPD over 10 h. Protein losses were not increased on TPD. In another study, comparing CAPD, CCPD, 50% TPD, and 25% TPD, therapy with 50% TPD plus wet days was found to be most efficient, but once again had the highest dialysate flow [133].

Studies utilizing roughly similar amounts of fluid have found no benefit of TPD in increasing solute clearances. For example, in the Spanish Multicenter Study [134], patients were treated with CAPD, CCPD, and TPD for 2 months each. The treatment volumes were comparable between CCPD and TPD and ranged from 14 to 15 L/night and 1.8 to 2.0 L/daytime. CAPD was found to have the lowest creatinine and urea clearances. CCPD had the highest urea clearances and creatinine clearances were comparable for CCPD and 50% TPD. A study comparing solute clearances and ultrafiltration on TPD and traditional IPD found with dialysate flow rates of 18.5 mL/min, solute clearances and ultrafiltration volumes were higher on IPD than on TPD. With flow rates of 25.9 mL/min, the ultrafiltration volume was higher on IPD, but no difference was found for solute clearance. At flow rates of 44.4 mL/min there was no difference in ultrafiltration or solute clearances between the two modalities [135]. Piraino et al. [136] in a small study using a dialysate flow rate of 3.7 L/h for IPD and 3.8 L/h for TPD found no difference in small molecule clearances. Quellhorst et al. [137] reported that TPD to be more efficient than IPD using a treatment volume of 60 L/day.

Middle molecule removal is a function of time and TPD has not been shown to impact clearances of β_2-microglobulin [138]. Sodium sieving is more marked in short dwell therapies, but the few studies analyzing sodium removal in TPD have found little differences from other APD modalities [86, 139, 140]. Quellhorst et al. [137] have documented better blood pressure regulation with TPD than IPD, while Balaskas et al. [141] found no difference.

In conclusion, TPD does not increase small solute clearances above those obtained with other APD therapies. The advantage of TPD with a continuous contact between the peritoneal surface and dialysis fluid may be offset by the negative influence of a smaller concentration gradient between dialysate and blood. It has been suggested that inadequate mixing of the tidal volume with the reserve volume may cause this. TPD may be indicated for patients experiencing pain at the beginning of inflow and/or the end of drain. It may also be used in patients with mechanical outflow problems such as due to adhesions or improper catheter placement [142, 143]. In such instances, a high initial fill volume with low tidal volumes may allow PD to continue sans problems. TPD may be the preferable modality for patients with ascites wherein controlled drainage of fluid can be achieved rather than draining the entire abdominal cavity with each cycle [144].

Breakpoint APD

Breakpoint APD is a TPD modality characterized by a variable reserve volume determined by the point at which the drain rates transition into a slow drain rate as discussed above in a previous section. The breakpoint may vary for an individual patient from cycle to cycle and with change in position, intraperitoneal pressure, and catheter function besides other factors. By transitioning from a drain phase to a fill phase at the "breakpoint," the time spent draining a limited quantity of dialysate would be eliminated, improving efficiency. Computerized modeling as well as clinical studies have shown improved clearances with this modality [86, 145]. In one study, shortening the total drain time to include only the initial high outflow period increased urea clearance by nearly 10% during an 8-h APD treatment with six cycles and a total dialysate flow of 12 L in a patient with average membrane permeability (urea MTC approximately 15 mL/min). The increase in urea clearance was the result of increased dwell time with maximal dialysate volume. There was also improved sleep quality due to decreased alarms [145]. In another study comparing NIPD, 50% tidal PD, and breakpoint APD, Amici found a 10% improvement in clearances with breakpoint APD compared to tidal [113].

Continuous Flow Peritoneal Dialysis

Continuous flow peritoneal dialysis (CFPD) is a futuristic modality to augment small solute clearances by maintaining a fixed intraperitoneal volume with a constant flux into and out of fresh or regenerated dialysate through the peritoneal cavity. This system allows the use of high dialysis flow to improve clearance values close to the MTC (Fig. 12.2). There is no time wasted during inflow and drain and a continuous concentration gradient generates a solute flux that is maintained during the whole dwell time [146, 147].

CFPD would offer an option a patient to remain on peritoneal dialysis after failure of CAPD or standard APD to provide adequacy. Cruz et al. [148] have demonstrated peritoneal clearances of 42 mL/min for urea and 33 mL/min for

creatinine using a dialysate flow rate of 200 mL/min and a 2-L initial fill volume. They obtained a mean ultrafiltration of 16 mL/min with a 1.5% dextrose solution. Raj et al. [149] using a single lumen catheter with a "Y" adapter and a lower dialysate flow rate of 141 mL/min obtained mean urea and creatinine clearances of 26.5 and 24.1 mL/min, respectively. An ultrafiltration of 3 mL/min was obtained with a mean dextrose concentration of 0.73 g/dL. Thus, an added advantage of CFPD is the ability to use lower dextrose concentrations as the system continuously adds dextrose to the system. Consequent reduction in glucose absorption may prevent complications attributable to high glucose concentrations in the dialysate. Because of the high efficiency of the treatment, patients could dialyze during the night and be dry during the day. Though this would potentially allow the peritoneal membrane to regenerate, there would be a loss of middle molecule clearances whose removal is time dependent and not flow dependent.

CFPD requires large amounts of fluid (200–300 mL/min) to achieve maximal efficiency. The use commercially available peritoneal dialysis solutions would be associated with enormous cost and storage issues. Recirculating a moderately sized batch of dialysate until it saturates, though an option, would limit clearances. Another approach is the online production of dialysate as done for hemofiltration, which would allow individualization of therapy. The most viable option may be the use of a commercial dialysate followed by continuous extracorporeal regeneration of the spent dialysate by either a hemodialysis filter or adsorption using a sorbent column or a combination of the two. The protein in the dialysate would be concentrated and returned to the patient in the final exchange [147]. This may be complicated by loss of middle molecule clearances since these are extensively protein bound [146].

Two catheters or a double-lumen catheter would be needed to provide such high flow rates of dialysate, with special designs to prevent streaming. Another issue that needs to be addressed with current cyclers is the inability to assess and control ultrafiltration. With CFPD, the ultrafiltered volume needs to be matched by removal of extracorporeal fluid. A mismatch would lead to either abdominal overdistension or underfilling. Segmental bioimpedance coupled with intraperitoneal pressure measurements with closed-loop feedback in intelligent machines may provide an answer in the future.

Nighttime Exchange Device

The nighttime exchange device (NXD) allows CAPD patients one or more nighttime exchanges while reducing patient burden and improving clearances (Fig. 12.7). Though several patients on four or less exchanges may opt for this device as a lifestyle choice, the NXD is extremely helpful for patients prescribed five or more exchanges [4].

There is a physiological and kinetic advantage to using this system. Equilibrium of urea between peritoneal dialysis solutions and plasma occurs within 3–6 h of dwell. Dwell times longer than 6 h do not contribute any further to the removal of small solutes and require higher concentrations of dextrose to maintain ultrafiltration. In terms of efficiency, four exchanges every 6 h are more effective than three short and one long dwell. The supine position for

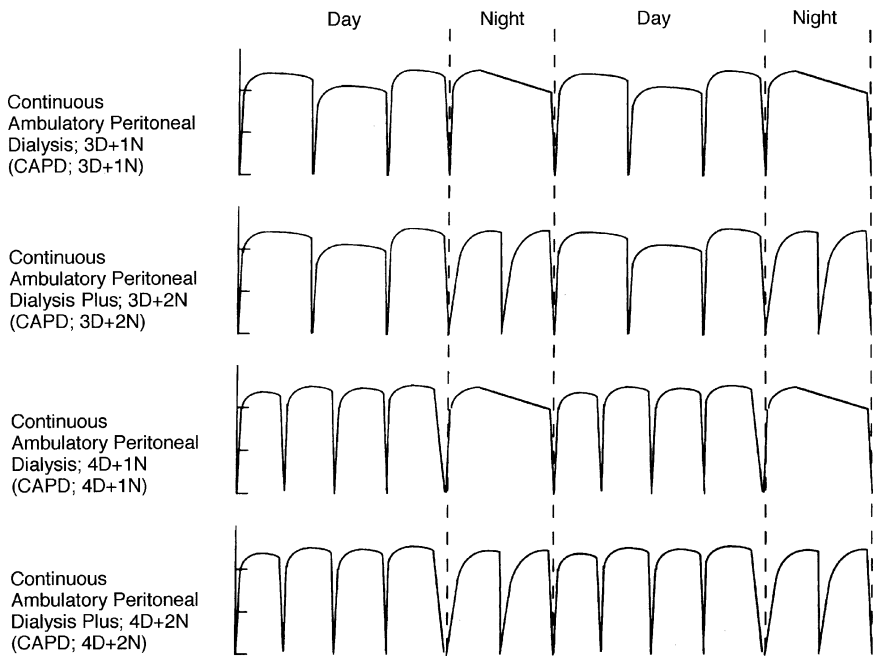

Fig. 12.7 Continuous ambulatory peritoneal dialysis (CAPD) and the use of the night exchange device (NXD). Panel 1 shows CAPD – three daytime exchanges and one bedtime exchange; panel 2 shows CAPD Plus – three daytime exchanges, one bedtime exchange, and an additional exchange delivered by the NXD; panel 3 shows CAPD – four daytime exchanges and one bedtime exchange; panel 4 shows CAPD Plus – four daytime exchanges, one bedtime exchange and an additional night-time exchange delivered by the NXD

the nighttime exchange(s) offers an opportunity to use higher V_{ip} maximizing the MTC without an increase in the IPP. Furthermore, patients retaining fluid due to the longer dwell at night on CAPD may also benefit from using the NXD. Patients switching to NXD only for lifestyle reasons, with no change in the number of exchanges, experience only a slight improvement in their solute clearances over baseline. In patients advised an additional exchange, the clearances increase significantly [150]. However, higher clearances may also be achieved by increasing the V_{ip} without changing the number of exchanges [81].

In summary, the major advantage of NXD is to help achieve adequacy in CAPD, as well in achieving net negative ultrafiltration in patients retaining fluid overnight [151].

Adequacy of Automated Peritoneal Dialysis

Background

Survival on dialysis is determined by the removal of nitrogenous waste products, correction of electrolyte and acid-base imbalance, and fluid removal to maintain normal volume status [152]. Adequate dialysis is defined as the dose of dialysis below which one observes a significant worsening of morbidity and mortality. The National Cooperative Dialysis Study (NCDS) [153] on hemodialysis gave rise to the concept that small solute clearances influence patient morbidity and mortality significantly, and these data were extrapolated to the peritoneal dialysis population.

Small solute clearances in peritoneal dialysis are conventionally quantified in terms of either urea clearance [Kt, (L/week)] normalized to total body water [V, (L)] and/or total creatinine clearance (C_{cr}) normalized to standardized body surface area (BSA).

A series of observational studies reported the importance of small solute clearances in defining adequacy among peritoneal dialysis patients [154, 155]. In 1997, the Kidney Disease Outcomes Quality Initiative (K/DOQI) Peritoneal Dialysis Work Group published a guideline for the adequacy of dialysis dose [156]. The K/DOQI recommended a weekly Kt/V of 2.0 in CAPD, 2.1 in CCPD, and 2.2 on NIPD. The initial creatinine clearance guidelines of 60 L/week/1.73 m^2 for all transport types were modified in the 2000 update of the guidelines to 50 L/week/1.73 m^2 for low and low-average transporters [157]. These guidelines were largely based on the results of the Canada-USA (CANUSA) study [155]; a reanalysis of this study showed that RKF predicted survival and not the peritoneal clearance [158]. Since then two randomized controlled studies in CAPD patients evaluating adequacy have been published. The ADEMEX (ADEquacy of peritoneal dialysis in MEXico) [159] found no difference in survival between groups having a mean total Kt/V of 2.27 and 1.80. Patients receiving a lower prescription had more deaths from congestive heart failure, uremia, and hyperkalemia. The Hong Kong study [160], a prospective randomized multicenter study, comparing three groups with total weekly Kt/V 1.5–1.7, 1.7–2.0, and >2.0 also did not find any difference in survival based on small solute clearances. The group with Kt/V of 1.5–1.7 had more anemia, inadequate dialysis, and ultrafiltration.

Observational studies in anuric CAPD patients suggest a minimum Kt/V urea of 1.7 as a minimum target. The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD), using time-dependent analyses of peritoneal clearances after achievement of anuria ($n = 130$) found no dose-response relationship between weekly Kt/V_{urea} and outcomes. Analyzing the data as a dichotomous variable, the investigators reported that a weekly $Kt/V_{urea} < 1.5$ was associated with an increased risk for death [161]. In an observational study from Hong Kong, patients at the onset of anuria with a baseline Kt/V_{urea} of less than 1.67 (based on a Kaplan-Meier analysis) had a significantly poorer patient survival, mainly confined to female patients [162].

No randomized controlled study addressing adequacy in APD has been performed. In a retrospective study involving a small sample of anuric CAPD and APD patients there was a trend to reduced mortality, although not statistically significant, in patients with peritoneal Kt/V urea above 1.85 [163]. Another study of 763 patients in which 34% of patients were on CCPD found that neither peritoneal Kt/V_{urea} nor peritoneal creatinine clearance were predictive of 1-year mortality [164]. The European Outcomes APD Study (EAPOS) [152] was a prospective multicenter study evaluating the feasibility and clinical outcomes of anuric APD patients ($n = 177$). Time-averaged creatinine clearance and baseline solute transport had no effect on patient or technique survival. Time-averaged analyses showed that age, subjective global assessment, and diabetic status predicted patient survival. Baseline ultrafiltration below 750 mL/day was predictive of poorer survival.

The above data establish the limitations of peritoneal small solute clearances in predicting outcomes of PD patients. Further, measured Kt/V_{urea} is not always the delivered Kt/V_{urea}. Nonadherence with exchanges, changes in timing of exchanges, variations in ultrafiltration volume, urinary output, and GFR may affect solute clearances. In addition, during automated peritoneal dialysis, the shorter nighttime exchanges provide a higher urea clearance than creatinine clearance.

Besides small solutes, protein-bound uremic toxins and middle-molecular-weight uremic toxins are important in the uremic syndrome. The removal of middle molecules is a function of the membrane area, membrane permeability, and time. Since time is the only variable, the total duration of dialysis is critical for the removal of middle molecule waste. Long dwells during the day contribute significantly to the clearance of middle molecules. The clearance of middle molecules in CCPD appears to be similar to CAPD. However, in NIPD with dry days, the time available for dialysis is reduced by 50%, and this dramatically reduces the clearance of middle molecules [126].

Several studies have demonstrated that peritoneal dialysis patients are overhydrated compared to hemodialysis and transplant patients [165, 166]. Furthermore, patients on APD have lower sodium removal and ultrafiltration than CAPD patients and consequently are more volume expanded [89, 91]. Some of the studies have been biased against APD because of not considering overfill of dialysis bags in their estimates [90]. The fluid status is associated with diastolic blood pressure, left ventricular hypertrophy, and mortality. The benefit of blood pressure and volume control has been demonstrated by Lameire [166]. Ates et al. [167] have demonstrated that better total sodium and fluid removal are factors effecting survival in peritoneal dialysis. In the EAPOS analysis, anuric patients on APD with baseline ultrafiltration below 750 mL/day had a poorer survival, but the effect of ultrafiltration disappeared in the time-dependent analysis [168]. Though greater fluid removal may indicate better volume control, it may also indicate a higher fluid intake. A higher fluid intake is more likely to be seen in healthier patients and the better outcomes with higher ultrafiltration and sodium removal may just be reverse causation [169].

Adequacy Recommendations

Guidelines from Kidney Disease Outcomes Quality Initiative (K/DOQI)

For patients with RKF (urinary volume >100 mL/day), the K/DOQI has recommended the minimum delivered dose of total small solute clearances (peritoneal and kidney), expressed as Kt/V_{urea}, should be at least 1.7 per week. Total solute clearances should be measured within the first month after initiating therapy and at least once every 4 months thereafter. If the patient has greater than 100 mL/day of urinary output, and RKF is being considered part of the total weekly clearance goal, a 24-h urine collection for urine volume and solute clearance should be obtained at a minimum of every 2 months. In patients with no RKF (urinary volume $\leq$100 mL/day), the minimum delivered dose of total small-solute clearance should be a peritoneal Kt/V_{urea} of at least 1.7 per week, measured within the first month of starting dialysis and at least once every 4 months thereafter [170]. Determination of creatinine clearance is no longer recommended for adequacy measurements by K/DOQI [164].

An emphasis on preserving RKF and maintenance of euvolemia is also incorporated into the guidelines. Important in preservation of RKF are the use of ACE inhibitors and angiotensin receptor blockers and avoidance of nephrotoxic exposure. Implementation of the goal of euvolemia involves close monitoring of urine volume, ultrafiltration, and physical examination including blood pressure. Restriction of salt and water intake, adjustment of the dialysis prescription as necessary, and use of loop diuretics to preserve or increase urinary volume are some suggested methods [170].

Other Guidelines

The International Society of Peritoneal Dialysis has made recommendations similar to the K/DOQI for small solute removals. Also recommended in APD patients is an additional target of 45 L/week/1.73 m^2 of creatinine clearance [171]. The European Best Practice Guidelines for PD recommend achieving a minimum Kt/V_{urea} of 1.7, a creatinine clearance of 45 L/week/1.73 m^2, and a net ultrafiltration of 1.0 L per day in anuric patients [172]. The Australian PD Guidelines advise the weekly Kt/V target should be =1.6/week. The minimum weekly corrected creatinine clearance (Ccr) target would be 60 L/week in high and high-average peritoneal transporters, and 50 L/week in low-average and low peritoneal transporters [173]. The Canadian Guidelines indicate that Kt/V_{urea} should be maintained at a minimum of 1.7 when the residual GFR is less than 4 mL/min. In patients with residual GFR greater than 4 mL/min, peritoneal Kt/V_{urea} may be maintained between 1.0 and 1.7.

The Automated Peritoneal Dialysis Prescription

The peritoneal dialysis prescription should take into consideration patient's body surface area (BSA), peritoneal membrane permeability properties, and amount of RKF. The presence of RKF makes it easier to achieve clearance

guidelines. Each 1 mL/min of corrected residual kidney creatinine clearance (C_{cr}) adds approximately 10 L/week/1.73 m^2 of creatinine clearance to the total C_{cr}. Similarly, for each 1 mL/min of urea clearance, 0.25 is added to the total weekly Kt/V for a 70-kg male. As the RKF declines with time the peritoneal dialysis prescriptions should be adjusted to maintain adequacy criteria.

The peritoneal transport characteristics are determined by the PET [69, 70], by mass transfer coefficients [71, 72], or by the standard permeability analysis [73]. The effect of peritoneal transport in influencing dialysis adequacy is both direct via solute clearance, and indirect via influencing ultrafiltration. A study assessing peritoneal transport characteristics of 1,229 patients found the group consisted of 15% low transporters, 33% low-average transporters, 37% high-average transporters, and 15% high transporters [94]. Low transporters are difficult to treat with APD unless they have substantial RKF. Body surface area and body weight affect the requirements for dialysis. Among the U.S. dialysis population, 75% of patients have a BSA >1.71 m^2 and a median BSA of 1.85 m^2.

The variables that may be manipulated in achieving adequacy are the dialysis modality, fill volume, number of exchanges and spacing, and duration of exchanges [129]. Computer-assisted kinetic modeling programs are available to help evaluate membrane transport characteristics and assist in writing prescriptions. Three major programs are available in the market: PD-Adequest® (Baxter Healthcare Corporation, Deerfield, Illinois, USA) [174], Patient-online (POL®) (Fresenius Medical Care, Bad Homburg, Germany) [175] and Personal Dialysis Capacity Test (PDC®) (Gambro, Lund, Sweden) [176]. These programs have user-friendly interfaces and use a mathematical model describing the peritoneal dialysis system. Data from a specific peritoneal function test needs to be entered for each patient [86, 177]. Even though prescriptions generated by the computer programs have reasonably close correlation with the actual measurement of 24-h urine and dialysate clearances, they are subject to errors. The errors relate to intraindividual biologic variability, population variability, lab errors and the use of peritoneal transport models that oversimplify the physiology of the peritoneal membrane. Furthermore, modeling expects a perfect performance of exchanges, which very often is not the case in real life [86]. Kinetic modeling is not meant to replace the actual measurement of clearance.

For a patient initiating APD with a residual GFR > 2 mL/min, the initial fill volume should range between 800 and 1,500 mL/m^2. The number of exchanges at night should be between three and five and the time on the cycler should range between 7 to 10 h. Dry days are not recommended except in patients with substantial RKF and in high transporters with small BSA. In anuric patients, higher doses of dialysis are required and low and low-average transporters with BSA exceeding 2.0 m^2 may not achieve adequacy with APD. Recommendations for initial therapy are summarized in Table 12.4, adapted from the National Kidney Foundation K/DOQI clinical practice guidelines for peritoneal adequacy: update 2000 [157]. General principles for APD therapy are summarized in Table 12.5.

The adequacy of the initial prescription must be assessed within the first month after initiating dialytic therapy and at least every 4 months thereafter. If the patient has a RKF that is being included in adequacy calculations, the RKF should be measured at a minimum of every 2 months. Inadequate dialysis may happen due to the dialysis prescription not being matched to the membrane transport characteristics, loss of RKF, insufficient time on the cycler or noncompliance, and a poorly functioning PD catheter.

The dialysis prescription can be optimized by increasing fill volumes. There is a theoretical linear relationship between body surface area and the volume of dialysate needed for optimal contact with peritoneal capillaries reaching a maximal at a fill volume of approximately 1,500 mL/m^2 [81]. Multiple studies have demonstrated that clearances rise as volume of dialysate is increased. In a study of 20 patients on either CAPD or APD, increasing fill volume by 1 L per

Table 12.4 Possible initial empirical dialysis prescriptions for CCPD

For patients with an estimated underlying GFR >2 mL/min	
BSA <1.7 m^2	4 × 2.0 L (9 h/night) + 2.0 L/day
BSA 1.7–2.0 m^2	4 × 2.5 L (9 h/night) + 2.0 L/day
BSA > 2.0 m^2	4 × 3.0 L (9 h/night) + 3.0 L/day
For patients with an estimated underlying GFR ≤2 mL/min	
BSA < 1.7 m^2	4 × 2.5 L (9 h/night) + 2.0 L/day
BSA 1.7–2.0 m^2	4 × 3.0 L (9 h/night) + 2.5 L/day
BSA > 2.0 m^2	4 × 3.0 L (10 h/night) + 2 × 3.0 L/day[a]

Source: NKF-K/DOQI Clinical Practice Guidelines for Peritoneal Dialysis Adequacy: update 2000 [157]

GFR = glomerular filtration rate; BSA = body surface area

[a] Consider combined hemodialysis/peritoneal dialysis or transfer to hemodialysis if the clinical situation suggests the need. These empirical prescriptions are based on modeling for patients with dialysate-to-plasma creatinine concentration ratio on PET of 0.71 at 4 h, BSA in the range above, and corrected residual kidney function of 2 mL/min or 0 mL/min

Table 12.5 General guidelines for APD therapy

1. Dialysis modality should be based on the ability of the regimen to provide adequate dialysis, the patients' preference, and their ability to perform the procedure.
2. APD prescriptions should be individualized based on membrane permeability, RKF, and BSA.
3. Computer prescription programs may be useful in designing prescriptions. Kinetic modeling, however, cannot replace actual clinical measurements of clearance.
4. Nightly intermittent peritoneal dialysis regimens should be avoided in all patients except high transporters with small body surface area or substantial RKF.
5. Anuric patients with low or low-average membrane transport characteristics should not be offered less than 24-h dialysis.
6. Delivered dose of dialysis and RKF must be periodically monitored. Prescriptions should be modified for a decline of RKF.
7. Clearances may be maximized by increasing the V_{ip} and/or the number of exchanges, minimizing drain time, and adding daytime exchanges.
8. Icodextrin may be used for the long dwell to improve clearances and ultrafiltration.
9. Compliance with prescriptions must be verified periodically.

RKF = residual kidney function; BSA = body surface area; V_{ip} = intraperitoneal exchange volume; IPP = intraperitoneal pressure

exchange increased urea and creatinine clearances by 26% [178]. In another study of CAPD patients, an increase in the dialysate fill volume of 1.5 L over 24 h increased peritoneal Kt/V_{urea} and creatinine clearance by 12% and 10%, respectively, and drain volumes by 20% [179].

Durand has recommended that fill volumes be optimized by monitoring of the IPP measured from the mid-axillary line, targeting a maximal of 18 cm H_2O [108]. These measurements should be done at atmospheric pressure. Whilst this is not a concern in disconnect systems, an air inlet is required for non-disconnect systems (such as APD) to negate the counter-pressure in the line and the empty bag. This is best achieved by introducing a trochar at the injection sit of the bag. On the other hand, Twardowski et al. [97, 180]. have demonstrated that there is poor correlation between IPP and tolerance of increased intraperitoneal volume. The best correlation of volume tolerance was with pulmonary function [97, 180]. Patients with the poorest tolerance of increased volume had a significant drop of the forced vital capacity at increased intraperitoneal volume with only small increase in IPP (Fig. 12.8). In a study from Mexico, even though

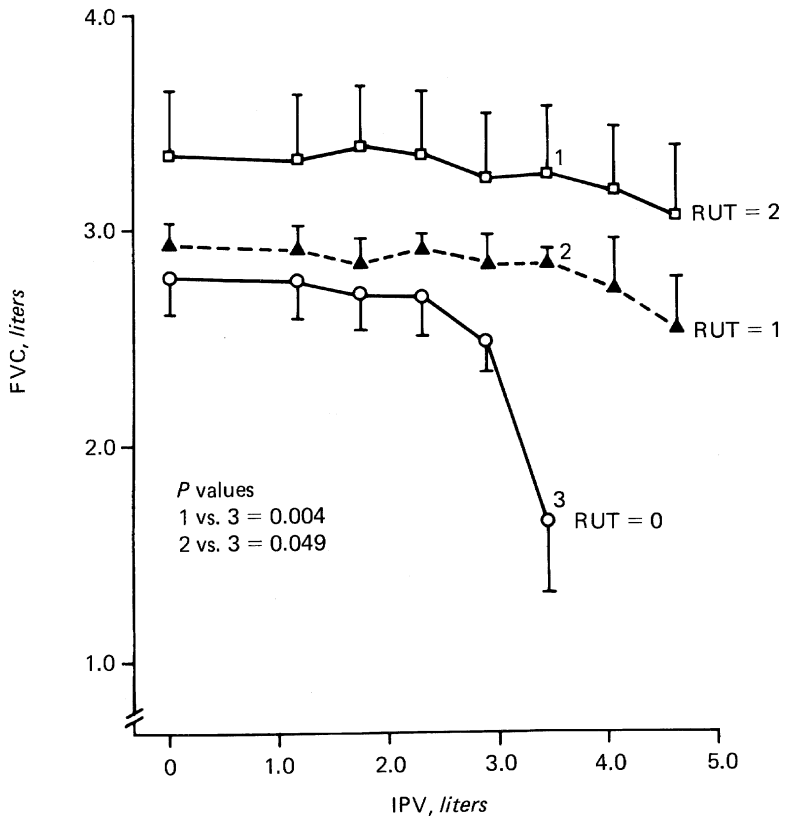

Fig. 12.8 Forced vital capacity (FVC) in the supine position in relation to intraperitoneal volume (IPV) in three groups of patients. Routine use of 3-L exchanges (RUT) = 2, patients routinely using 3-L volume exchanges; RUT = 1, patients occasionally using 3-L volume; RUT = 0, patients never using 3-L volume. From Ref. [97] with permission

larger dialysate volumes caused more discomfort, there was a lack of correlation between the discomfort score and the IPP [109]. The discomfort score was determined by asking patients to mark on a visual analog score their level of discomfort. When a 2.0-L dialysate volume was infused, the discomfort score for 86% of the patients was lower than 10, and that for 93% was lower than 50. With a 2.5-L dialysate volume infusion, 64% of patients had a discomfort score lower than 10 and 83% lower than 50. With a 3.0-L dialysate volume infusion, 44% of patients had a discomfort score lower than 10 and 64% lower than 50 [109]. Sarkar et al. [178] have shown that few patients are capable of discriminating between 2.0-, 2.5-, and 3.0-L dialysate volumes when infused blindly in random order. Most patients did not complain of discomfort in the face of a documented increase in their abdominal perimeter when 3.0 L of dialysate was infused. Thus, a majority of patients will be asymptomatic with higher fill volumes.

An alternative to increasing the fill volume is increasing the number of exchanges. More frequent cycling theoretically increases the time spent in filling and draining. A study by Perez et al. [140] evaluated this issue by comparing four different APD regimens for 1 week each. The prescriptions were for 9 h each and were all based on 2-L dwell volumes, but differed in the frequency of exchanges. They were 5 × 2 L, 7 × 2 L, and 9 × 2 L, as well as a 50% tidal peritoneal dialysis (TPD) prescription using 14 L. Higher dialysate flow rates achieved a higher small solute clearance across all membrane transport types as well as better ultrafiltration and sodium removal. The peritoneal urea clearance was significantly higher using 9 × 2 L exchanges as compared to the other three prescriptions. The peritoneal creatinine clearance was the lowest, with 5 × 2 L, and comparable between 7 × 2 L and 9 × 2 L therapies. The urea and creatinine clearances on TPD exceeded only those obtained with 5 × 2 L and were comparable to the 7 × 2 L regimen. Juergensen [181] has also reported that peritoneal Kt/V_{urea} and peritoneal creatinine clearance increase significantly when the frequency of exchanges and the total volume are increased across all transport types. Frequent cycling may negate the effects of lost time by the benefits of more frequent replenishment of the peritoneal cavity, with fresh dialysate maximizing diffusive clearance and the better-maintained osmotic gradient leading to better ultrafiltration. Such a regimen increases the cost of therapy and may be useful in some patients who cannot do a day exchange or tolerate a higher fill volume.

The use of daytime exchanges is more advantageous and cost effective. Based on kinetic modeling, Blake et al. [130] have demonstrated that in CCPD, addition of a daytime exchange is superior to further increases in the nightly dialysate volume (Fig. 12.9). In anuric patients, one to two daytime exchanges are required to meet the adequacy guidelines [152] unless one uses "high-flow" APD [182]. Increasing the time on the cycler is another option to achieve adequacy. The patient's lifestyle must be kept in consideration prior to modifying duration on the cycler. Compliance typically decreases if the total cycle time exceeds 9 h per session [183].

Management of Ultrafiltration

Volume overload is associated with congestive heart failure, left ventricular hypertrophy, and hypertension and is a predictor of poor survival [170]. It is therefore important to achieve a desirable target weight in a peritoneal dialysis patient where the patient is euvolemic. The edema-free state can be considered the minimum bracket for euvolemia. The weight below which undesirable clinical signs and symptoms such as hypotension and cramps develop can then be viewed as the maximum bracket for fluid removal. The weight range between these defined limits constitutes the

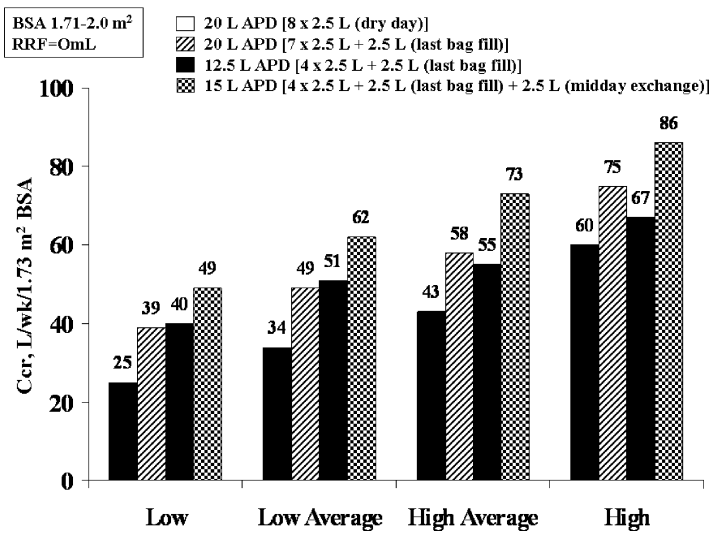

Fig. 12.9 The effect on creatinine clearance of wet days, increasing the number of exchanges, and adding a midday exchange to APD therapy prescriptions. The difference compared with a dry day is illustrated clearly in the first two bars of each membrane transport type. The effect of a midday exchange is shown in the last bar. From Ref. [130] with permission

clinical definition of desired weight – a highly variable and often complex target [184]. Maintenance of euvolemia requires attention to the peritoneal transport characteristics, protection of RKF, dietary counseling and enhanced compliance, use of loop diuretics, and control of hyperglycemia [94]. APD creates a biphasic profile for clearance and ultrafiltration with short nocturnal exchanges and a long daytime dwell. The shorter dwells provide for higher ultrafiltration rates because of a higher initial dextrose concentration. The membrane transport characteristics have a minimal effect on ultrafiltration with short dwells, while in the long dwell fast transporters have negative ultrafiltration [94]. Attention to the long dwell is essential in achieving euvolemia. If inadequate or negative ultrafiltration is seen, a midday exchange or switch to icodextrin must be considered [151]. Use of hypertonic glucose-based solutions that may cause peritoneal membrane damage should be minimized.

As regards the short dwells, frequent cycling could increase the inactive time and decrease net ultrafiltration but this has not been borne out in clinical studies [140, 181]. APD offers a unique ability to alter the tonicity of the dialysate by using bags of different tonicities since the cycler draws proportionally on all bags selected for a given

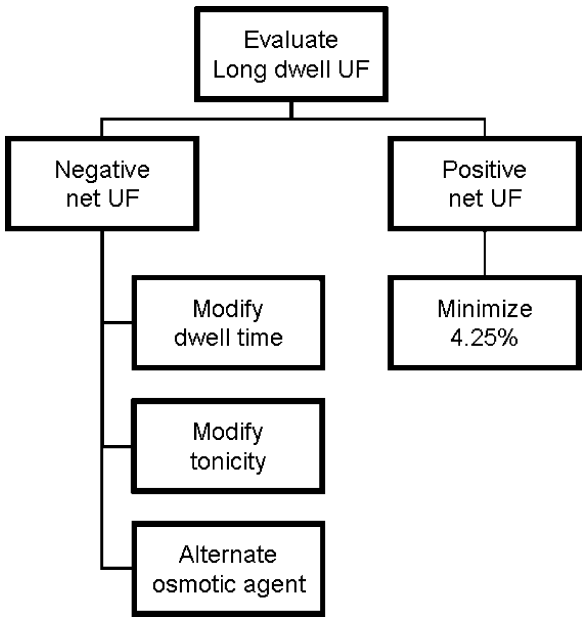

Fig. 12.10 Algorithm for fluid management in patients on PD: Management of the long dwell. UF: ultrafiltration. Modified from Ref. [151] with permission

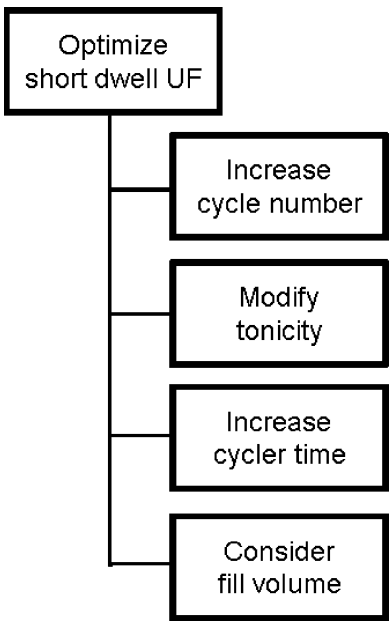

Fig. 12.11 Algorithm for fluid management in patients on PD: Management of the short dwell. UF: ultrafiltration. Modified from Ref. [151] with permission

therapy. For example, equal mixing of a 1.5 and 2.5% dextrose solution can create a 2% dextrose solution. The caloric cost per milliliter of ultrafiltration is lower with the use of higher tonicities of dextrose [151]. An increase in the fill volume helps increase ultrafiltration because of a higher total glucose mass in the peritoneal cavity [185]. However, increasing fill volumes increases IPP and may enhance net fluid absorption [110], though the effects are likely to be modest with short dwell times in APD [151]. An algorithm for fluid management in APD is detailed in Figs 12.10 and 12.11.

Incremental Peritoneal Dialysis

The decision to initiate dialysis was until recently based on the development of uremic symptoms or complications. It is becoming conventional now to start dialysis earlier to have a healthy start and avoid malnutrition and uremic complications. It is suggested that one could initiate dialysis with a "full-dose" prescription, ignoring the residual kidney component, or alternatively, one could "incrementally" increase the dialysis component of solute clearance as RKF decreases, maintaining minimal total solute clearance goals at all times [170].

APD offers an option for incremental peritoneal dialysis. Patients with significant RKF may be initiated on NIPD. With decline in RKF clearances may be augmented by switching to high-dose NIPD or to CCPD. Later, clearances may be improved by combining APD with CAPD (Fig. 12.12) [186]. Theoretically, such an approach could protect the peritoneal membrane from 24-h glucose exposure. Early start of peritoneal dialysis is associated with some risks. These risks include infection and a quicker loss of RKF. There is also the possibility that increasing the length on peritoneal dialysis may contribute to eventual patient "burn out". The reduced interference with daily routine, lower work burden, and fewer complications with APD make this a preferable procedure for early start.

Monitoring of Treatment

Patient compliance with therapy may be monitored by use of removable memory cards, teledialysis, reviewing order histories, and by frequent home visits. Catheter malfunction may be suspected if there are frequent alarms and by observing the fill/drain profiles. Changes in serum creatinine should make one suspect a change in RKF, changes in peritoneal transport characteristics, or noncompliance. Direct measurements of RKF are mandated by guidelines every 2 months and of peritoneal clearances every 4 months [170]. Since APD treatments are intermittent in nature, a fluctuation in plasma concentrations predialysis versus postdialysis may be seen. These differences are more marked for urea than creatinine and postdialysis samples will overestimate Kt/V [187]. To standardize measures of Kt/V, the blood sample should preferably be obtained at a time equidistant from the previous and subsequent nocturnal APD session.

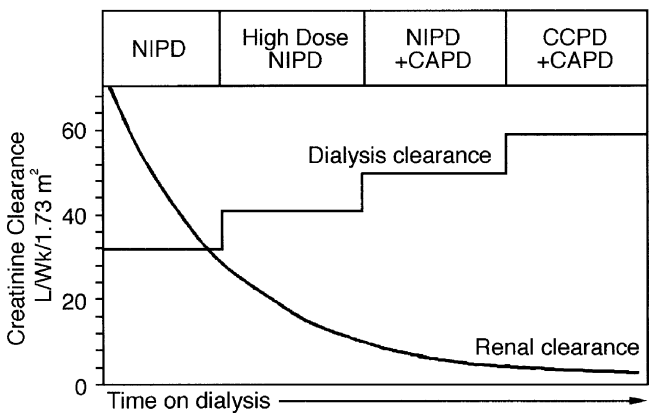

Fig. 12.12 Schematic drawing showing the adaptation of APD to change in residual kidney function. From Ref. [186] with permission

Complications of APD

Qualitatively, the complications of APD are similar to those encountered with CAPD. However, quantitative differences may exist in the incidence of these complications in the two modalities. Here, we will discuss selective complications of APD.

Peritonitis

Although the incidence of peritonitis in patients treated with peritoneal dialysis has decreased during recent years, it remains a major complication and frequent cause of hospitalization and discontinuation of peritoneal dialysis. The incidence of peritonitis in the earlier years of APD was significantly lower than CAPD [26, 188–190]. With the introduction of disconnect systems, the incidence of peritonitis has markedly decreased on CAPD. Some studies continue to demonstrate a benefit of APD over CAPD. In a randomized prospective study, de Fijter and associates [191] observed that peritonitis occurred significantly less often in those patients receiving CCPD than in those on CAPD with Y-connectors (0.51 compared with 0.94 episode per patient-year; $p = 0.03$). The median time to the first episode of peritonitis was 11 months for patients receiving CAPD with Y-connectors compared with 18 months for CCPD patients ($p = 0.06$). Patients on CAPD with Y-connectors developed their second episode of peritonitis in 6 months compared to 25 months for CCPD patients ($p = 0.18$). Rodriguez-Carmona [192] also reported on the superiority of APD over CAPD in regards to peritonitis. The adjusted difference was 0.20 episodes/patient/year.

In contrast, Burkart et al. [193], in another prospective study, found no difference in the incidence of peritonitis between patients on APD (0.58 episode per patient-year) and patients on the Y-set (0.61 episode per patient-year). Their patients using the standard spike system developed peritonitis at a significantly higher rate of 1.62 episodes per patient-year. Williams and co-workers [194] reported the incidence of peritonitis on APD to be similar to CAPD with disconnect systems with one episode occurring every 31 months and 29 months, respectively. The incidence of peritonitis for CAPD without disconnect systems was one in 13 months. Yishak et al. [195] reported peritonitis rates of 0.57 per patient-year and 0.55 per patient-year on APD and CAPD, respectively. A report of the French Peritoneal dialysis registry [8] reported a lower incidence of peritonitis on APD. However, the data is hard to interpret since the patient populations were somewhat different. Patients needing nursing assistance, overall a sicker population, more often received CAPD with nondisconnect systems and a majority of autonomous patients received APD. Oo and colleagues [196] in a recent retrospective analysis of the USRDS database between 1994 and 1997 found CAPD to be associated with a lower risk of development of a first episode of peritonitis after 9 months of peritoneal dialysis therapy as compared to CCPD. Even though this data set did not include information on connectology, it is likely that most patients would have been on a Y-system (with or without a twin-bag).

In studies showing benefit of APD over CAPD, the reduced numbers of connections to, and disconnections from, the abdominal catheter have been thought to be significance [191, 192]. Furthermore, most of these connections in APD occur between two sterile surfaces (a new connection line and a new bag); while in CAPD, most connections are between the new set and a reusable transfer line and peritoneal catheter. Improved patient technique due to performance of all connections in the same environment, less patient fatigue due to performance of fewer connections, and assistance of a helper may help reduce peritonitis rate. Most APD systems now employ flush-before-fill technology, further reducing infection by touch contamination. In addition, peritoneal immune function may be better preserved in patients with dry days in NIPD or having long dwells on CCPD [37, 197].

Patients with peritonitis usually present with cloudy fluid and abdominal pain. A dialysate white blood cell count $>100/mm^3$, with more than 50% polymorphonuclear cells, is supportive of the diagnosis, as is a positive Gram stain. The number of cells in the effluent will depend in part on the length of the dwell. Patients on APD with a day dwell who present during the day generally have cell counts similar to those of CAPD patients and are not difficult to interpret. However, APD patients without a daytime exchange who present with abdominal pain may have no fluid to withdraw. In this case, 1 L of dialysate should be instilled and allowed to dwell for at least 1 h, and then drained and examined for turbidity and sent for cell count, differential, and culture. In equivocal cases, or in patients with systemic and abdominal symptoms in whom dialysate appears to be clear, a second exchange is performed with a dwell of at least 2 h but preferably 3–4 h. On occasions, the initial drain of stagnant fluid present in the abdomen all day in patients with only partial daytime exchanges or dry days will appear cloudy in the absence of peritonitis. The white blood cell count may exceed $100/mm^3$, but

mononuclear cells will predominate. More important, dialysate rapidly clears with the initiation of peritoneal dialysis. Clinical judgment should guide initiation of therapy [198].

For patients on APD who present during their nighttime treatment, the dwell time is much shorter than with CAPD; in this case, the clinician should use the percentage of polymorphonuclear cells rather than the absolute number of white cells to diagnose peritonitis. The normal peritoneum has very few polymorphonuclear cells; therefore, a proportion above 50% is strong evidence of peritonitis, even if the absolute white cell count does not reach 100/mL [198].

The diagnosis of peritonitis in APD may often be delayed in patients using cyclers that dispose of dialysate directly without a drain bag [199]. To avoid those problems, patients should be trained to collect a small amount of the dialysate from the initial drain at the start of the night therapy and inspect it for cloudiness. If abdominal pain is experienced, a manual exchange for inspection and possible cell count with culture is recommended.

The organisms causing peritonitis in APD are similar to CAPD [191, 195, 200]. *Pasteurella multocida* has been identified as the cause of peritonitis in a few patients. This infection is caused by cats biting into the cycler tubing [201].

Intraperitoneal antibiotics, used intermittently or continuously, are preferred to intravenous antibiotics for treatment of peritonitis. Most antibiotics have enhanced absorption during peritonitis. For successful intermittent intraperitoneal therapy, high concentrations of the drug must be achieved in the systemic circulation, of sufficient magnitude that enough drug will diffuse back into the dialysate in subsequent drug-free exchanges [202]. With rapid exchanges in APD, there may be inadequate time to achieve therapeutic intraperitoneal levels with subsequent exchanges using intermittent antibiotics. Little is known about the pharmacokinetics of antibiotics and treatment outcomes in APD. Further, most of the studies performed in APD have been done on uninfected patients with intravenous administration of antibiotic, which makes it hard to extrapolate the data to intraperitoneal treatment of peritonitis [203–205]. The data show the clearance of antibiotics is largely dependent on dialysate flow as well as the RKF [202].

Among the data available, cefazolin, cefepime, and ceftazidime used once daily do not provide an adequate minimum inhibitory concentration of antibiotic during short nighttime cycles for most organisms [206–208]. Similarly, vancomycin in a dose of 15 mg/kg given intravenously also does not provide adequate intraperitoneal levels [205]. Oral ciprofloxacin in a dose of 750 mg twice a day provides dialysate concentrations that exceed the MIC for *Escherichia coli* and *Klebsiella* sp, but below those needed for *Pseudomonas aeruginosa* [209]. In spite of this pharmacokinetic data, clinical studies using intermittent antibiotics on APD have provided cure rates between 73 and 88%, catheter removal rates of 7.5–17.5%, and peritonitis-related deaths of 2–10%, which is not different than CAPD [210].

The International Society of Peritoneal Dialysis in its recommendations for treatment of peritoneal dialysis infections: 2005 Update [198] has suggested that vancomycin, cefazolin, tobramycin, fluconazole, and cefepime may be administered intermittently while continuing APD. The recommended doses are mostly higher than those for CAPD and a minimum 6-h dwell time for the antibiotic containing dialysate is advised. The committee also acknowledged the inadequacy of data backing these recommendations. Given this lack of knowledge, alternative options for treatment are switching patients to CAPD, using longer cycles on APD, or continuous antibiotics. Each institution should consider modifying the guidelines for initial antibiotic therapy based on their data on common organisms and sensitivities. In addition, patients may require adjustment of the APD prescription to account for the increased permeability of the peritoneal membrane during peritonitis.

Catheter Infections (Exit Site and Tunnel)

Catheter-related infections are an important cause of morbidity, peritonitis, and catheter failure. There appears to be little difference in the incidence of catheter-related infections on APD in comparison to CAPD. In data reported by Burkart et al. [193], the incidence of exit-site infections was 0.41 episode per patient-year for APD, 0.32 per patient-year for patients on Y-sets, and 0.62 per patient-year for patients on a standard spike. Statistical significance was only seen for the comparison between Y-set and standard spike ($p = 0.01$). de Fijter et al. [191] and Rodriguez-Carmona et al. [192] reported a similar incidence of exit site infections between APD and CAPD. Holley and coworkers [211], on the other hand, reported a significant decrease of exit-site infections for cycler patients (0.5 episode per patient-year) in contrast to CAPD patients using disconnect systems (0.86 episode per patient-year). Patients on nondisconnect systems developed exit-site infections at an incidence of 1.2 episodes per patient-year. Overall, disconnect systems, including APD, have fewer catheter infections than nondisconnect systems. It may be

postulated that, by disconnecting, the exits are subject to lesser trauma, tension, torque, or pulling [193]. The assessment and management of exit site and tunnel infections in APD is no different from CAPD.

Complications of Increased IPP

Hernias and Dialysate Leaks

The most common anatomic complication of peritoneal dialysis is hernias. The usual sites for these are sites of previous abdominal incisions and the umbilical, inguinal, and pericatheter regions [212]. The incidence of hernias on CAPD ranges between 10 and 25%, while on IPD the incidence is 2–5%; for CCPD the incidence is approximately 9% [213, 214]. The higher pressures in sitting and standing as against in the supine position may be partly responsible for this difference [97]. However, in spite of the fact that IPP rises proportional to the infused volume, there is no consensus between studies whether higher fill volume increases the incidence of hernias and leaks. In a survey of 75 dialysis units, representing 1864 dialysis patients across the United States and Canada, Van Dijk et al. [212] found no association between the volume of dialysate and the time of the largest exchange with the development of hernias. Similarly, Del Paso et al. [215] and Hussain et al. [216] found no association between fill volume and hernias. Furthermore, Durand et al. [217] found no relationship between IPP and mechanical complications. It may be possible that the IPP required to cause hernias are much higher than achieved under usual clinical conditions, and patients who develop hernias have structural weakness of the abdominal wall. Susceptible patients include older multiparous females, patients with autosomal dominant polycystic kidney disease, those with prior hernias or dialysate leaks, and prolonged corticosteroid treatment [212, 215, 218]. Susceptible patients should receive smaller diurnal dwells. Surgery is recommended for most hernias because of the risk of bowel or omental incarceration and strangulation. Post-surgery, once patients return to peritoneal dialysis, low volume and/or supine dialysis should be used.

Dialysate leaks are another frequent complication and occur more often in CAPD than APD. Risk factors for development of leaks are the median insertion of the peritoneal dialysis catheter, increased intra-abdominal pressure, and a weak abdominal wall. Leaks are characterized by dissection of fluid through tissue planes and may or may not be associated with hernias. These may present as abdominal or genital edema, pericatheter pseudohernias, and rarely as a vaginal leak of dialysate. Leaks may be a cause of ultrafiltration failure and weight gain [219]. Fluid leaks may be detected by radionucleotide imaging, MR peritoneography, or by computerized tomography scans with contrast in the dialysate [220]. Sometimes, leaks without associated hernias resolve by utilizing low-volume supine dialysis or a temporary transfer to hemodialysis. Surgical repair may eventually be required.

Respiratory Function

The presence of fluid in the abdomen and elevated IPP impact on pulmonary indices. There is a greater decline in pulmonary indices in the supine position compared to the upright or sitting positions [97]. CAPD patients generally have better pulmonary indices than patients do on APD. A good measure of the tolerance of intraperitoneal volumes is the forced vital capacity (FVC) in the sitting position [97, 180] and supine position [97, 217] (Fig. 12.8). Thieler et al. [221] described that the FVC in the supine position declined by a mean of 3.4% after the infusion of 2 L of dialysate into the peritoneal cavity. Pulmonary indices were not significantly affected by the presence of 2 L of fluid in the sitting or upright positions. In a study by Durand et al. [108], vital capacity decreased linearly by 4.42% per liter of V_{ip} in the supine position. During sleep, the drop in vital capacity is reflected by a reduction in the pulmonary reserve volume. Decreases in vital capacity by 20% or more may affect blood oxygenation. It has to be stressed that some patients may feel discomfort and shortness of breath at lower intraperitoneal volumes, possibly due to the reduced strength of the diaphragm [96, 111]. Caution needs to be exerted in increasing fill volumes on APD in patients with lung disease. The ultimate guide of the appropriate intraperitoneal volume is the subjective assessment of the patient [97, 180].

Hydrothorax

Hydrothorax is another pulmonary complication. Hydrothorax usually develops on the right side. Patients may range from being asymptomatic to having severe respiratory compromise. Most patients developing hydrothorax are females; multi-parity confers an additional risk. Fluid transverses the diaphragm through lymphatics or through defects in the diaphragm [219]. This complication occurs very rarely on NIPD and may be treated by low-volume supine dialysis, pleurodesis, or surgical repair [222].

Back Pain

Back pain is another complication related to increased IPP. The increased IPP can pull lumbar vertebrae into a more lordotic position and increase the stress on the spine. Poor muscle tone, osteoporosis, and degenerative joint disease can worsen the process. The treatment is aimed at reducing IPP by switching to APD, preferably with dry days [214].

Residual Kidney Function

The RKF contributes significantly to the adequacy of dialysis and the excretion of middle and large molecules. Survival on peritoneal dialysis has been linked to the RKF [158, 164]. Various studies have explored the loss of RKF in APD patients. An analysis of the Dialysis Morbidity and Mortality Study (DMMS) found no difference in the decline of RKF between APD and CAPD although ultrafiltration rates were not reported [223]. Hamada et al. [224]. reported better preservation of renal function in APD patients in a small study with a two-year follow-up. A prospective, nonrandomized study of 53 new CAPD and 51 APD patients followed for at least 1 year found a faster rate of loss of RKF in APD patients, despite controlling for PET results. This difference may have been negated by the role of ultrafiltration in determining loss of RKF and may have been influenced by prescription alterations once PET results were known [225]. In a small nonrandomized study of new dialysis patients, Hiroshige et al. [226] found that RKF declined more rapidly in APD patients over a 6-month period. For the eight patients on NIPD, the rate of decline in creatinine clearance was -0.29 mL/min/month and for the four CCPD patients -0.34 mL/min/month. These rates were significantly higher compared to the authors' own CAPD data, as well as the data of others. In another prospective, small nonrandomized trial of 36 consecutive unmatched new PD patients followed over 1 year, there was a faster rate of decline in the APD group. The APD group consisted of both CCPD and NIPD patients without any difference in the rate of loss for each therapy, although the numbers were small [227]. It is suggested that the acute changes in volume status and osmotic load induced at each nightly PD session could potentially accelerate deterioration of RKF.

Technique and Patient Survival in APD

Peritonitis and catheter related infections are the leading cause of technique failure on peritoneal dialysis. Other causes include mechanical catheter problems, inadequate dialysis including ultrafiltration failure, and psychosocial problems. In 1984, Diaz-Buxo et al. [19] had reported the technique survival for CCPD to be 80%, 62%, and 56% at 1, 2, and 3 years, respectively. A more recent study by Mujais et al. [10] examined the profile of PD practice in the United States by following four large inception cohorts of patients starting PD in the years 2000–2003. This study found that transfer to HD was lower in APD than CAPD for any cause of technique failure. This difference was most evident in the first year on PD and tended to disappear during the second year of therapy. Overall technique survival in APD was 81% in the first year and 67%, 55%, and 46% in each of the 3 subsequent years in this study. Patients on CAPD had a significantly higher rate of technique failure in the first 6 months and stabilized thereafter. Overall, technique success was 75% in the first year and 63%, 53%, and 44% in each of the 3 subsequent years for CAPD [10]. Patients treated with APD have a survival advantage over CAPD in the first 6 months of therapy. A younger age, selection bias of patients for APD, or better compliance with therapy may have influenced patient survival on APD in this study. The overall trend is of improving patient outcomes and technique success with time. The European APD Outcome Study was a prospective multicenter study of outcomes on APD in anuric patients. Patient survival was 78% and technique survival 62% and combined patient and technique survival was 49% at 2 years. The predictors of poor survival were age >65 years, malnutrition, diabetic status, and ultrafiltration <750 mL/day [152]. Peritoneal membrane transport had no effect on survival, though the study excluded low transporters [152].

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