Chapter (29)

Factors Affecting Peritoneal Dialysis Dose

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CHAPTER OUTLINES

- Concept of Dose and Adequacy in Peritoneal Dialysis (PD)
- Patient-Specific Factors Affecting Chronic PD Dose
- Prescription-Specific Factors Affecting Chronic PD Dose
- Factors Affecting PD Dose in the Treatment of Acute Kidney Injury
- Conclusion

CHAPTER OBJECTIVES

- To review the concept of and evidence for dose and adequacy in PD
- To understand the various physiological and sociological patient-specific factors affecting achieved PD dose
- To understand the various PD modalities, prescription-specific factors affecting dose
- To review the various factors and PD technique considerations in the treatment of acute kidney injury

KEY TERMS

- dialysis dose
- adequacy
- effective peritoneal surface area
- membrane transport characteristics
- residual urine function
- body surface area and weight
- compliance
- PD modality
- exchange frequency
- fill volume
- ultrafiltration
- middle molecule clearance
- acute kidney injury

ABSTRACT

Dose of dialysis has traditionally been measured as small solute clearance (i.e. urea or creatinine). Treatment of acid-base, electrolyte, and volume disturbances should also be recognized as important functions of peritoneal dialysis (PD) that are not specifically measured when measuring urea clearance. There are a myriad of patient- and prescription-specific factors that affect the delivered dose of PD. Although patients with significant residual renal function (RRF) can likely initiate on virtually any

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standard PD therapy, with loss of RRF, one may need to tailor the PD prescription to the patient's membrane transport characteristics. High transporters as measured by the PET are better suited to automated peritoneal dialysis (APD) with more frequent exchanges, and the use of icodextrin as a long dwell, whereas patients with lower transport status will tend to do well on CAPD where exchanges are longer. Larger patients may tolerate increased volumes as a means of increasing the dose of PD. More frequent exchanges can be used in either CAPD or APD but one must recognize there is a limit due to loss of dialysate contact time from frequent filling and draining. Understanding the patient's physiological characteristics, personal preferences and social circumstances coupled with a sound comprehension of the principles of PD and the prescription-factors that affect dose will lead to the best care for that patient.

29.1 CONCEPT OF DOSE AND ADEQUACY IN PERITONEAL DIALYSIS

This chapter will review the factors that influence dose of peritoneal dialysis (PD). Those in the dialysis community routinely use the terms *prescription* and *dose* when speaking of dialysis and more specifically, PD. This brings to mind the analogy of prescribing a medication such as an ace inhibitor. One provides a prescription to a patient that outlines the medication name, how many tablets are to be included, how often the patient is to take it, and the *dose* of the medication. The *dose* is usually measured by mass and/or number of pills (i.e. one 5 mg tablet). The efficacy of achieving the desired effect – i.e. lowering of blood pressure – will vary between patients for a given dose.

The term *dose* in peritoneal dialysis is not as straightforward. One of the earliest references to *dose* of dialysis in PD was by Twardowski in 1989 in the context of the clinical value of the peritoneal equilibration test (PET) in patients (Twardowski 1989). He suggested that patients with low transport status may need “high-dose PD prescriptions”. Later Blake and colleagues evaluated the effects of *dose* of PD on clinical outcomes: dose was measured by the dialysis index (a now seldom used measure determined using urea kinetic modeling) and the more well-known Kt/V_{urea} (Blake et al. 1991). Still others have simply defined the *dose* of dialysis as the drain volume – i.e. the total amount of fluid removed from the patient which is the sum of instilled dialysate plus ultrafiltrate (Tzamaloukas et al. 2007). This would seem reasonable in continuous ambulatory PD (CAPD). The weekly measured peritoneal Kt/V for urea (pKt/V_{urea}) is defined as:

$$pKt / V_{urea} = \frac{7 \times (D / P_{urea}) \times V_D}{V} \quad (29.1)$$

where K is solute clearance, D/P_{urea} is the ratio of dialysate to plasma concentration of urea in 24-hours of collected dialysate, V_D the drain volume, and V is total body water.

With the longer dwells used in CAPD (as opposed to automated PD [APD]) one can assume that D/P_{urea} approaches unity so that Eq. (29.1) can be simplified to (Heimburger 2009):

$$pKt / V_{urea} = \frac{7 \times V_D}{V} \quad (29.2)$$

Assuming V is equal to 58% of weight (Wt) in kilograms one can then expresses Kt/V as a function of body weight and drain volume:

$$pKt / V_{urea} = \frac{12 \times V_D}{Wt} \quad (29.3)$$

The relationship between drain volume, body size, and estimated pKt/V_{urea} is shown for a number of scenarios in Table 29.1 below.

Table 29.1 Relationship between drain volume, body size, and estimated pKt/V_{urea}

Weight (kg)	Fill volume (L)	Number of exchanges	Drain Volume (L)	pKt/V_{urea}
50	2.0	4	8.0	1.92
50	2.0	3	6.0	1.44
75	2.0	4	8.0	1.28
75	2.5	4	10.0	1.60
65.4	2.0	4	8.0	1.47

The latter example represents the average weight for patients in the control group of the ADEMEX study (Paniagua et al. 2002) (described in more detail later), all patients were on 2.0-L x 4 exchanges. Measured pKt/V_{urea} was actually about 7.5% higher at 1.58, the difference presumably due to a combination of errors in assumptions about equilibration of urea, total body water estimation, and collection and measurement errors. Nevertheless, it does illustrate the point that for patients on CAPD with four or fewer exchanges, the drain volume is a useful tool to estimate the

dose of dialysis when taking into account the patient's weight. It should be noted that while one could increase the number of exchanges to increase the pKt/V_{urea}, the assumption that the urea concentration will equalize between dialysate and plasma becomes increasingly inaccurate as exchanges become shorter.

The assumption that urea will equilibrate between dialysate and plasma during an exchange (and therefore one can predict pKt/V_{urea} based on drain volume and body weight) is particularly problematic with patients on APD. One can craft a number of different scenarios where the total dose (i.e. drain volume) received is the same yet what is achieved in terms of the various functions of dialysis – small solute removal including phosphate, volume removal, middle molecule removal – will actually differ. Three examples for APD are shown in Table 29.2. Total therapy ranges between 9-hours and 24-hours and ultrafiltration volume from 1.0-L to 1.5-L in the examples. Nevertheless drain volumes in each of the scenarios is 15.5-L. Small solute clearance may well be similar in these scenarios, depending on membrane transport properties etc., other aspects of adequacy such as fluid removal and middle molecule clearance will not be.

Table 29.2 Three different APD prescriptions with the same drain volume

	Patient 1	**Patient 2**	**Patient 3**
Modality	APD	APD	APD
Night-time therapy, hours	9	9	10
Night-time fill volume, L	2.0	2.5	2.0
Number of cycles	7	5	5
Day-time therapy, hours	0	4	14
Day-time volume, L	0	2.0	4.0 (manual exchange)
Ultrafiltration volume, L	1.5	1.0	1.5
Total drain volume, L	15.5	15.5	15.5

For these and other reasons, the fact that *dose* in PD is usually defined by small solute clearance such as urea, is not completely satisfactory. The nephrologist and PD nurse must recognize that this viewpoint largely ignores other functions of dialysis and consider these issues when prescribing PD therapy. The most recent Canadian Society of Nephrology guidelines on hemodialysis (HD) have noted this fact.

> "Urea clearance as assessed by Kt/V or PRU is a surrogate for dialysis dose. Although practice guidelines have traditionally emphasized the role of urea clearance, this parameter is only one component of dialysis adequacy. In addition to considering urea clearance and volume status, the clinician must consider many other measures and indicators in assessing a patient's health and prescribing treatment, including control of extracellular volume and BP, uremic symptoms, quality of life, control of hyperphosphatemia, adequate nutritional status, and treatment of anemia."(Jindal et al. 2006)

The term 'adequacy' is perhaps more familiar to most dialysis providers and was described in the context of PD as early as 1976 by Lindsay and colleagues (Lindsay et al. 1976). Platelet adhesion was noted to be markedly impaired in uremia and it was suggested that platelet adhesion could be used as a measure of dialysis adequacy. A number of studies in the late 1970s and early 1980s characterized neurological abnormalities in uremia including changes in memory and characteristic electroencephalographic changes that improved to a greater extent with more intensive dialysis (Shinaberger 2001; Teschan 1975; Teschan et al. 1981). These objective measures are no longer used clinically in the day-to-day management of patients and adequacy becomes more of a subjective concept. Many nephrologists would define adequacy to represent that amount of delivered dialysis that alleviates uremic symptoms (nausea, anorexia, fatigue etc.), restores acid-base balance, achieves fluid homeostasis, and alleviates malnutrition. Such a definition would seem equally appropriate for hemodialysis (HD) and PD patients. Other aspects of adequate treatment of ESRD might include correction of hyperphosphatemia, hypocalcemia, vitamin D deficiency and anemia; however, these complications are less responsive to dialysis with some exceptions (Ifudu et al. 1996; Ifudu et al. 2000; Movilli et al. 2001; Walsh et al. 2010).

As time has gone on, it has become increasingly apparent that when one considers adequacy one must consider all aspects of the PD prescription (i.e. mode of PD, total time, exchanges, fill volume etc.) in order to achieve the desired results in a given patient based on their individual characteristics, particularly transport status and residual renal function (RRF). Ultimately, it stands to reason that one should evaluate the delivery of dialysis as *adequate* when increasing the dialysis dose does not lower the mortality risk and/or further improve quality of life (Golper et al. 1997). No single measurement can truly measure the adequacy of dialysis. Published guidelines recognize this yet based on the best evidence and/or

opinion generally advises a lower limit for small solute removal (i.e. Kt/V_{urea}) in patients to achieve adequacy.

Numerous observational studies suggested that greater clearances of small solutes were associated with improved survival on PD (Bhaskaran et al. 2000; Churchill et al. 1998; Jager et al. 1999; Jansen et al. 2005; Lam et al. 2006; Lo et al. 2005; Maiorca et al. 1995; Rumpsfeld et al. 2009, 2006), although others have not (Brown et al. 2003; Diaz-Buxo et al. 1999). The CANUSA study (Churchill et al. 1998) in particular led to the recommendation of a target total Kt/V_{urea} of 2.0 (peritoneal plus renal) in guidelines although this was based on inferences from modeling of data that assumed RRF and peritoneal clearance were equivalent. Since then these findings have subsequently been shown to be largely explained by the presence or absence of RRF (Bargman et al. 2001). However, two important randomized controlled trials have since shown that increased small solute clearance was not associated with improved survival (Lo et al. 2003; Paniagua et al. 2002). ADEMEX in particular was very telling – 965 CAPD patients were randomized to 2.0-L x 4 exchanges or an increased volume of dialysate (Paniagua et al. 2002). There was no benefit in either group studied despite good separation in clearance values (pKt/V_{urea} 1.62 vs. 2.13). Approximately 55% of patients were anuric.

Despite all the concerns in limiting the view of adequate PD therapy as simply sufficient small solute removal, it remains important to consider the factors that affect dialysis dose in PD. It is clear that some amount of PD therapy is clinically important, recent guidelines have suggested a minimum Kt/V_{urea} of 1.7 (Blake et al. 2011). Although peritoneal clearance does not appear to predict clinical outcomes in patients with RRF, clearance does seem to be important in patients who are anuric based on the majority of observational studies (Bhaskaran et al. 2000; Jansen et al. 2005; Lo et al. 2005).

It is worth reminding the reader that there are two main PD modalities available to patients – CAPD and APD. CAPD is the simpler of the two, involves manual exchanges of fluid using gravity, and it is performed over 24 hours. Although the timing of the exchanges could be varied to achieve different desired effects; usually only the fill volume (standard is 2.0-L) and the number of exchanges (standard is 4 although 3 is used in some countries) (Lo et al. 1996) are varied to achieve different doses of dialysis. APD on the other hand is amenable to greater variation in prescription. The therapy can be continuous or discontinuous (i.e. part or all of the daytime is dry), the number of exchanges overnight and the duration of the cycles manipulated as can be the volume. In either the case of CAPD or

APD, one can vary the prescription by altering the dialysate used to achieve differing ultrafiltration rates.

In the subsequent sections, the various factors that affect dose in PD will be reviewed. These are broken down into patient-specific and prescription-specific factors. The special case of clearance of middle molecules and PD in the treatment of AKI will also be considered.

29.2 PATIENT-SPECIFIC FACTORS AFFECTING CHRONIC PD DOSE

29.2.1 Peritoneal Membrane

The abdominal peritoneum is divided into the visceral peritoneum, which lines the visceral organs and accounts for approximately 80% of the total surface area; and the parietal peritoneum which lines the remainder of the abdominal cavity (Albanese et al. 2009; Bouchet 1989; Fischbach et al. 2003; Pawlaczyk et al. 1996; Rubin et al. 1988). Functionally in PD, the parietal peritoneum appears to be more important than the visceral peritoneum (Flessner 1991). The peritoneal membrane consists of three anatomical components: a single mesothelial cell layer, the interstitium which is composed of mucopolysaccharide matrix and bundles of collagen fibers, and the capillary wall (Flessner 1996b, 1991). The peritoneal microvasculature is comprised of true capillaries and post capillary venules, while most of the lymphatic drainage is through stomata located in the diaphragmatic peritoneum. For a more in-depth discussion on the topic of peritoneal anatomy, functional structure, or physiology, please refer to previous chapters.

Peritoneal transport comprises three simultaneous processes: diffusion, ultrafiltration, and fluid absorption (Burkart 2000). There is now cumulative evidence supporting the view that the major site of resistance to peritoneal transport is provided by the peritoneal capillary and is likely the key determinant of transport capacity (Flessner 1996b; Krediet 2000a). The mesothelium is no longer considered an important transport barrier (Flessner et al. 2003; Krediet et al. 1993). Furthermore, the barrier function of the interstitial tissue is not well known (Flessner 1996b).

The three-pore model of peritoneal transport is a simple simulated computer model that for the most part, adequately describes peritoneal permeability and selectivity (Rippe et al. 1991; Rippe et al. 2004). Using this model, the capillary endothelium contains three distinct types of pores. The major exchange route for water and solute is through a large number of “small pores” (radius 40-50 Angstroms), corresponding to paracellular clefts in the endothelium (Bundgaard 1984). Small pores account for 95%

of the hydraulic conductance and functionally for approximately 50% of the effective ultrafiltration (Fusshoeller 2008). A second very small population of "large pores" (radius 250 Angstroms), likely representing interendothelial clefts serve as the transcapillary pathway for albumin and other large proteins (Rippe et al. 2004). The third population consists of the abundant "ultra-small pores" (radius 3-5 Angstroms) that are responsible for the transport of solute-free water across the capillary wall. Ultra-small pores have been predicted to mediate 40 to 50% of the ultrafiltration and the "sodium sieving" observed during a dwell with hypertonic dextrose. Aquaporin-1 (AQP1), a protein belonging to a family of integral plasma membrane proteins has been found to be the molecular counterpart of the ultra-small pores (Devuyst 2010; Devuyst and Ni 2006).

29.2.1.1 Effective Peritoneal Surface Area

In adults, the anatomic surface area is approximately equal to the body surface area, ranging from 1.0 to 2.0 m^2 (Albanese et al. 2009; Nagy 1996). However, during a session of PD, the entire peritoneum is not in contact with dialysate to partake in solute and water transport. Moreover, the peritoneal surface area that is in contact with dialysate participates to varying degrees, determined primarily by the peritoneal vascularity (Krediet et al. 1994). This has led to the term, "effective peritoneal surface area" which emphasizes the importance of peritoneal membrane vascularity over its anatomic surface area. The effective peritoneal surface area is the product of the vascular peritoneal surface area and the permeability (also referred to as size selectivity). In turn, the vascular peritoneal surface area is dependent on the peritoneal surface area in contact with dialysate (PSA-CD) and on the density of perfused capillaries (Chagnac et al. 1999). Using stereologic methods applied to CT scans of the peritoneal membrane, the PSA-CD was estimated to be 0.55 m^2 (25 to 30% of the anatomic surface area) in adult PD patients (Chagnac et al. 1999). An increase from a 2.0 to 3.0-L dwell volume was associated with an 18 % increase in the PSA-CD from a mean value of 0.57 to 0.67 m^2, and in a 28% increase in the mass transfer area coefficient (MTAC) for creatinine from 10.6 to 13.6 ml/min. The MTAC is also known as the permeability-surface area product and is equal to the theoretical clearance of a solute that would be achieved if the concentration gradient was always infinitely high. The MTAC is typically calculated with the aid of a computer program,

$$\mathrm{MTAC} = \frac{V_D}{t} \times \ln\left(\frac{P - D_0}{P - D_t}\right) \tag{29.4}$$

where V_D is the drain volume, t is the dwell time (240 minutes), P is the plasma concentration, D_0 is the dialysate concentration before inflow, D_t is the dialysate concentration at the end of the dwell (Krediet et al. 2000a). Although the effective surface area cannot be measured directly, it can be characterized by the MTAC of creatinine, expressed as ml/min (Krediet et al. 1993).

The transport of macromolecules such as serum proteins are size-selectively restricted, and thus determined by both the effective surface area and permeability (size-selectivity) of the peritoneum. On the contrary, the transport of low-molecular-weight solutes is not hindered by the intrinsic permeability of the peritoneum and is therefore mainly dependent on the effective surface area (Krediet et al. 1994). Consequently, changes in the D/P ratios of small solutes and in the MTAC reflect changes in the effective surface area (Krediet et al. 1993). The effective surface area can increase markedly in certain situations, such as, peritonitis, ultrafiltration failure following chronic PD, and following intraperitoneal administration of nitroprusside, a vasodilator (Douma et al. 1997; Krediet et al. 1987, 2000a).

29.2.2 Peritoneal Blood Flow

The visceral peritoneum receives its blood supply from the superior mesenteric artery and drains into the portal system while the parietal peritoneum receives its blood supply from the lumbar, intercostal, and epigastric arteries and its venous drainage is through the inferior vena cava (Bouchet 1989). The number of perfused peritoneal capillaries is dynamic and varies with changes in splanchnic blood flow, although a direct relationship is unlikely (Aune 1970).

Under physiological conditions, peritoneal blood flow (estimated between 50 and 100 ml/min) does not limit the transfer of solutes, as the MTAC for urea and creatinine are 17 and 10ml/min, respectively (Flessner and Lofthouse 1999; Heimburger et al. 1992; Rosengren and Rippe 2003; Waniewski et al. 1992). This is demonstrated by the finding that a reduction in blood flow by hemorrhagic hypotension resulted only in a marginal decrease in urea and creatinine clearance (Erbe et al. 1967; Greene Jr et al. 1970). It is important to note that the "effective blood flow" available is only a fraction of the total blood flow through the tissues surrounding the peritoneal cavity because some capillaries are too far from the mesothelium to be active in the exchange process or they are in a part of the peritoneum not in contact with dialysate (Flessner 1996a, b). Moreover, there is evidence indicating that perhaps peritoneal blood volume rather than blood flow *per se*, determines the degree of peritoneal mass transfer (Pietrzak et al. 1989).

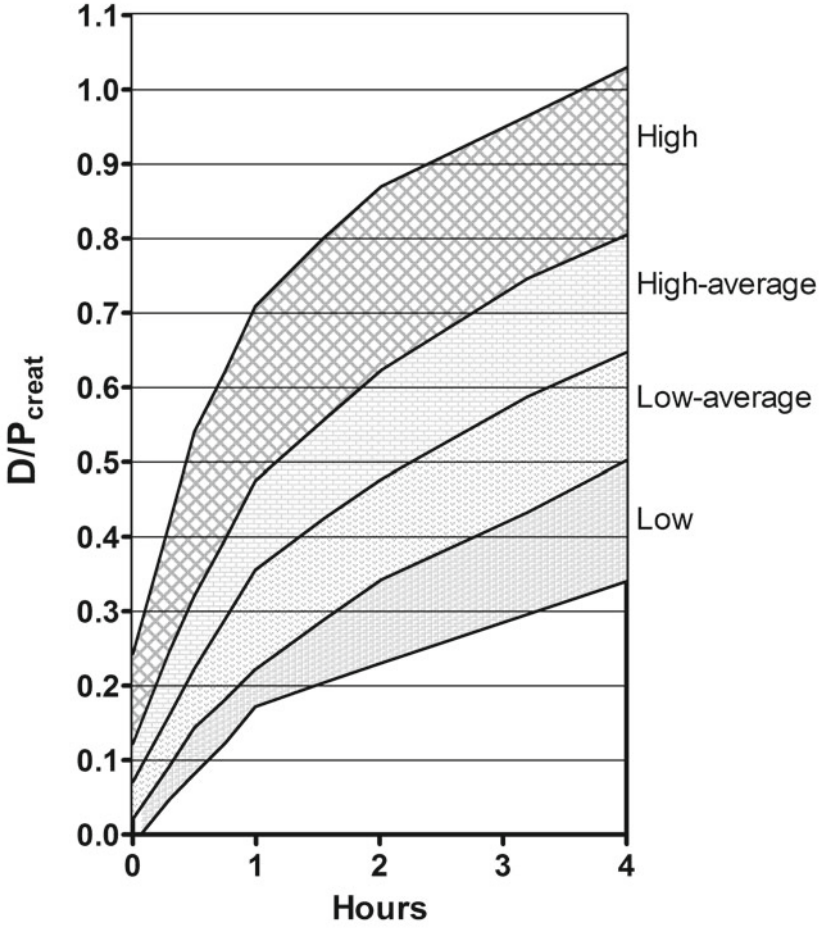
Therefore, in PD, the clearance of small solutes is not limited by peritoneal blood flow, but rather, dialysate flow (Flessner and Lofthouse 1999).

29.2.3 Peritoneal Equilibrium Test

First described in 1987 by Twardowski, the peritoneal equilibration test (PET) is the most widely used standard test for evaluation of peritoneal transport characteristics, specifically solute transport and ultrafiltration capacity, which are fundamental in guiding the PD prescription (Twardowski et al. 1987). There is considerable variability in membrane transport properties between-patients and within-patients over time. The goals (van Biesen et al. 2010) of evaluating peritoneal membrane transport are: 1) To optimize the PD prescription with respect to small solute clearance, volume management, and treatment of uremia; 2) To evaluate peritoneal membrane function over time; 3) To assess other membrane characteristics, such as, osmotic conductance of glucose, aquaporins, lymphatic reabsorption, hydraulic conductance (in patients with ultrafiltration failure).

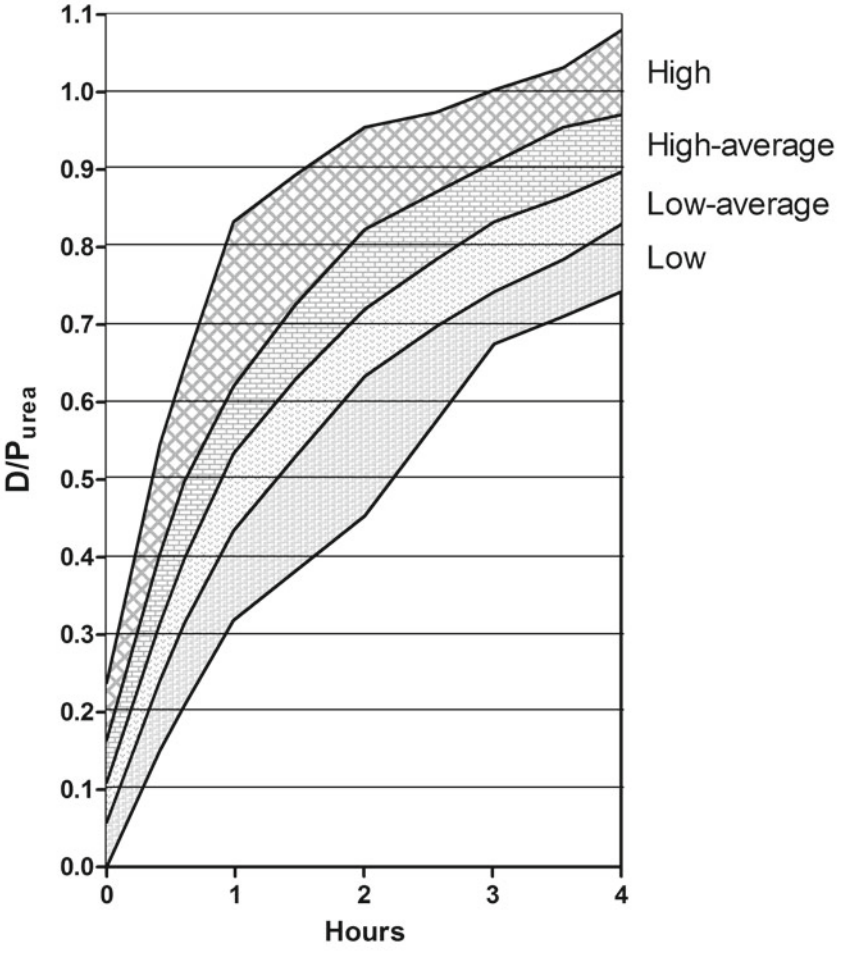
This semi-quantitative assessment is influenced by the molecular weight of the solute of interest, membrane permeability, and the peritoneal effective surface area. There is far less between-patient variability in the peritoneal clearance of urea due to its more rapid equilibration between dialysate and plasma than with creatinine at 4-hours as illustrated in Fig. 29.1 (more narrow distribution of the D/P_{urea}-time curve). As such, the 4-hour peritoneal clearance of creatinine is used to characterize the small-solute transport characteristics of the membrane. Conventionally, the PET test is performed with 2.0-L of 2.5% dextrose solution for a 4-hour dwell. The technical aspects of the test are outlined elsewhere (Twardowski et al. 1987). Equilibrium ratios (D/P) between dialysate and plasma for urea (D/P urea), and creatinine (D/P creatinine) are calculated at 4-hours. For glucose, D/D_0 glucose is calculated to determine the fraction of absorbed glucose from the dialysate at 4-hours to the initial dialysate glucose concentration (D_0). Peritoneal transport status is then classified into one of four membrane categories based on the 4-hour D/P creatinine: High, High-average, Low-average, and Low. High transporters (defined as a D/P creatinine greater than +1 standard deviation [SD] from the mean) have the highest D/P creatinine and the lowest D/D_0 glucose (< -1 SD from the mean). Conversely, low transporters (defined as a D/P creatinine less than -1 SD from the mean) have the lowest D/P creatinine and the highest D/D_0 glucose (> +1 SD from the mean). In 90% of properly conducted PETs this inverse relationship between D/D_0 glucose and D/P creatinine is observed (Prowant et al. 2010). The PET is also used to measure the net ultrafiltration. Ultrafiltration volumes correlate positively with the 4-hour D/D_0 glucose and negatively with D/P creatinine. A baseline PET

study is performed shortly after a patient has been established on PD and can be repeated routinely (i.e. yearly) based on local practice patterns or when there is clinical suspicion of change in membrane transport characteristics (i.e. hypervolemia, malnutrition, metabolic disturbances). Consideration of individual patient-specific peritoneal membrane characteristics (small solute clearance and ultrafiltration capacity) will allow nephrologists to tailor a PD prescription to meet the needs of the patient.



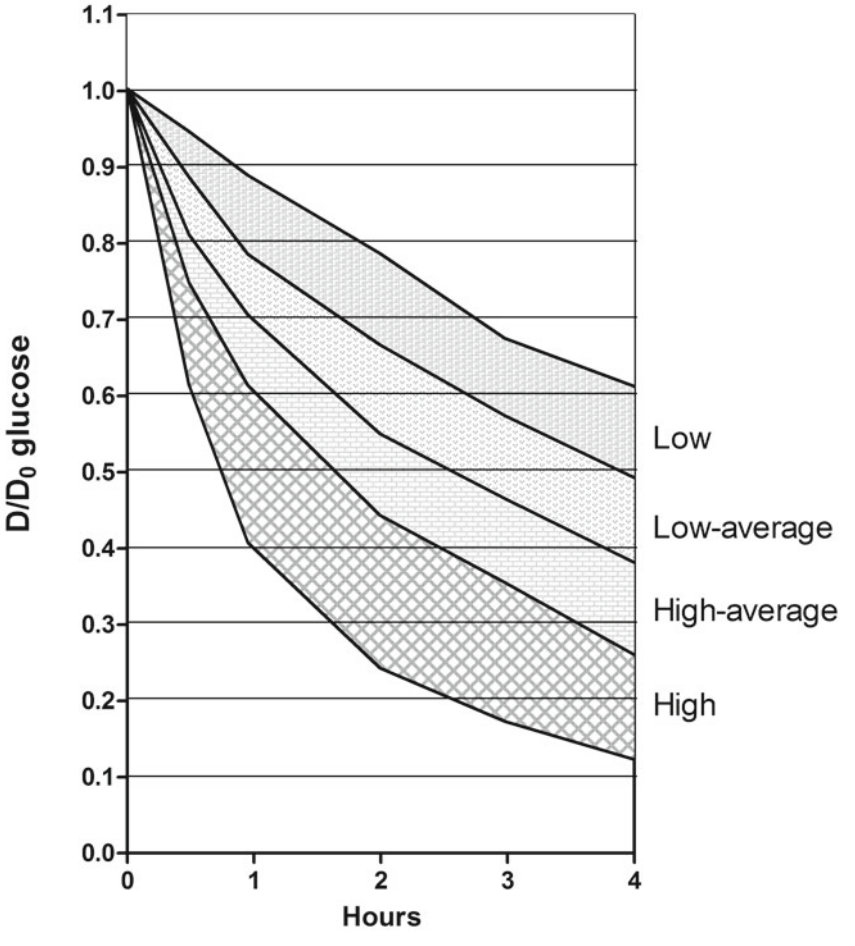
(a)

Fig. 29.1 Standard peritoneal equilibration curves for (a) creatinine, (b) urea, and (c) glucose absorption showing ranges for High, High-average, Low-average, and Low transporters. (Adapted from Twardowski ZJ, et al. Peritoneal equilibration test. Perit Dial Bull 1987:7:138)



(b)

Fig. 29.1 (Continued)



(c)

Fig. 29.1 (Continued)

29.2.3.1 Peritoneal Membrane Transport Status

As originally described by Twardowski (Twardowski et al. 1987), peritoneal membrane transport status is classified into one of four transport categories. However, it has been proposed that the classification should be changed to three categories that may be more intuitively related to the dwell time (van Biesen 2010): Fast, Average, and Slow transporter status. In the discussion that will follow, the classification as it was originally

described by Twardowski was used but the reader should be aware of this alternative classification used in the literature.

29.2.3.1.1 High Transporters

High transporters have a relatively larger effective peritoneal surface area or higher intrinsic membrane permeability and achieve the most rapid diffusive transport, resulting in the highest D/P creatinine values (Li and Chow 2007). This also explains the observation of higher dialysate protein losses and lower serum albumin values. However, high transporters have the lowest D/D_0 with reduced ultrafiltration capacity owing to more rapid dissipation of the glucose osmotic gradient and resultant negative ultrafiltration in dwells with 1.5% dextrose for longer than 3 hours (Perl et al. 2009; Mujais et al. 2000). High transporters dialyze well with respect to small solute clearance but ultrafiltration poorly and are best suited for PD prescriptions with short dwells, preferably less than 3-hours. The convenience of APD in performing frequent exchanges with short dwell times makes this modality the ideal choice for High transporters. For High transporters who choose to do CAPD due to lifestyle preferences, such as, sleep disturbance from the cycler, consideration for the use of icodextrin for the long night dwell should be given, especially when there is loss of RRF.

Amongst the four transporter types, High transporters have been associated with the highest mortality (Rumpsfield et al. 2006; Brimble et al. 2006; Churchill et al. 1998; Fried 1997). This was best demonstrated in a meta-analysis by Brimble et al (Brimble et al. 2006) that included 19 studies (9 prospective) in PD patients with PET data and mortality and/or technique failure outcomes. Compared to patients with low transport status, High transporters had a 77% increased mortality risk (RR 1.15 for every 0.1 increase in D/P creatinine, $P<0.001$); a finding that was present in studies from diverse geographic regions and in patients with a variety of comorbidities. There was a trend towards death-censored technique failure in those with higher transport status (D/P creatinine) that did not meet statistical significance ($P=0.12$). Furthermore, studies that enrolled patients on APD demonstrated a lower mortality risk for a given increase in peritoneal membrane solute transport rate compared with those that did not, suggesting APD may be more appropriate for High transporters. Possible mechanisms for the adverse outcome seen in High transporters include: protein losses leading to malnutrition, volume overload, inflammation, and greater systemic exposure to glucose.

An observational study by Johnson et al (Johnson et al. 2010) using data from the Australia and New Zealand Dialysis and Transplant (ANZDATA)

registry also suggested that the higher mortality associated with High transporters can be abrogated by the use of APD.

The ANZDATA registry included data from 4128 incident PD patients who started PD between 1999 and 2004, of which 628 were High transporters. There were 486 patients in the CAPD and 142 in the APD group. Compared to High transporters treated with CAPD, APD-treated High transporters were more likely to be Caucasian (P=0.006), younger (P=0.003), and less likely to have diabetes (P=0.03). Mean baseline PET D/P_{4hr} creatinine was comparable between the APD and CAPD groups (0.88 vs. 0.87, P=0.15). On multivariate intention-to-treat analysis, treatment with APD was associated with superior survival (adjusted HR 0.56, P=0.01) and comparable death-censored technique survival (HR 0.88, P=0.4). There were no statistically significant differences in patient survival or death-censored technique survival between APD and CAPD for High-average and Low-average transporters. Conversely, Low transporters treated with APD compared to CAPD had a higher mortality rate (HR 2.19, P=0.04). One of the main limitations of this study was the lack of adjustment for RRF due to incomplete data collection.

Randomized controlled trials supporting the use of APD to improve clinical outcomes in High transporters are lacking. A randomized open-label trial (Bro et al. 1999) comparing APD and CAPD in 25 prevalent PD patients with High or High-average transporters showed statistical difference in net ultrafiltration, Kt/V_{urea} and creatinine clearance, but was not powered to evaluate patient or technique survival. A meta-analysis by Rabindranath included 3 randomized controlled studies of APD versus CAPD involving 139 patients with different transport status, including the study above (Bro et al. 1999) and found no difference in patient or technique survival. However, the meta-analysis lacked statistical power and subgroup analysis was not undertaken in High transporters (Rabindranath et al. 2007).

29.2.3.1.2 Low Transporters

Low transporters have low membrane permeability or a small effective peritoneal surface area, resulting in a lower D/P creatinine that is semilinearly correlated with the dwell duration. Serum albumin values tend to be higher since dialysate protein losses are lower. The D/D_0 glucose values are higher resulting in excellent net ultrafiltration that peak late in a long dwell. There is sustained ultrafiltration even in dwells longer than 4 hours. Low transporters benefit from higher volumes (see section on Fill Volumes in CAPD and APD) and continuous regimens, such as CAPD

(Burkart et al. 1996). Low transporters are more difficult to treat with APD unless they have significant RRF.

29.2.3.1.3 High-Average and Low-Average Transporters

The equilibration of creatinine for "Average" transporters is moderately fast, with a steeper equilibration slope in the beginning than at the end of a dwell. Ultrafiltration capacity is also intermediate. Dwell times less than 2 hours and longer than 7.5 hours should be avoided except for one exchange per day (the "long dwell") (van Biesen et al. 2010).

In clinical practice however, patient lifestyle and preferences are the main driving force for choice of PD modality rather than peritoneal transport characteristics. Most patients, irrespective of their membrane transport status can be managed successfully the majority of the time with APD or CAPD, especially when they have RRF. However, when RRF is lost over time, the PD prescription (dwell time) should be chosen to match the peritoneal transport characteristics if targets for solute clearance and/or ultrafiltration are not achieved (see Table 29.3).

Table 29.3 Peritoneal equilibration test results, ultrafiltration, and preferred PD modality (Twardowski et al. 1987; Birkart et al. 1996)

Transport Status	4-hr D/P creatinine	Ultrafiltration	Preferred PD Modality
High	> 0.81	Poor	APD
High-average	0.65 to 0.81	Adequate	APD/CAPD
Low-average	0.50 to 0.64	Good	APD/CAPD
Low	< 0.50	Excellent	CAPD

Membrane transport characteristics can change over time. Some patients develop histomorphological and functional changes of the peritoneal membrane during long-term PD and following recurrent episodes of peritonitis (Davies et al. 2011). Typical morphological changes during PD include the loss of mesothelium, sub-mesothelial fibrosis, angiogenesis, vasculopathy, and basement membrane duplication (Fusshoeller 2008). Chronic exposure to glucose based PD solutions, glucose degradation products, and resulting advanced glycation end-products are the most important factors contributing to the development of fibrosis and a large effective surface area (Krediet et al. 2000b; Fusshoeller 2008). Based on biopsy registry data, high-volume APD patients tended to have more

peritoneal fibrosis after less time on PD, pointing to a cumulative dose exposure effect (Fusshoeller 2008).

The functional peritoneal alterations include impaired transport of water and solute. Ultrafiltration failure is defined clinically as net ultrafiltration < 400 ml over a 4-hour dwell with 3.86% dextrose and affects approximately 35% of all PD patients after 4 years of treatment (Smit et al. 2004). Ultrafiltration failure is classified into four types (which can overlap) based on the underlying pathophysiology (Fusshoeller 2008): type 1 - large effective peritoneal surface area; type 2 - low osmotic conductance to glucose; type 3 - low effective peritoneal surface area; and type 4 – high effective lymphatic absorption rate.

The most frequent cause of ultrafiltration failure is a large effective peritoneal surface area with resultant hyperpermeability of the membrane (type 1) (Fusshoeller 2008). There is rapid dissipation of the osmotic gradient (from rapid glucose absorption) leading to less fluid removal and/or fluid absorption. The use of icodextrin and shorter dwell times with APD may help to maintain adequate ultrafiltration. Strategies for the prevention of ultrafiltration failure include: the avoidance of excessive glucose exposure, preservation of RRF, and prevention of peritonitis (Davies et al. 2011).

29.2.4 Residual Renal Function

Randomized trials of dialysis adequacy and observational studies in adult patients have confirmed that RRF is a stronger predictor of patient survival than PD dose (Bargman et al. 2001; Lo et al. 2003; Paniagua et al. 2005). In the CANUSA study, a prospective observational study of incident peritoneal dialysis patients, each 5 L/week of RRF was associated with a 12% reduction in the relative risk of death (Bargman et al. 2001). Subsequent studies have shown a consistent association between RRF and lower rates of adverse cardiac outcomes, including left ventricular hypertrophy and congestive heart failure (Wang et al. 2002; Wang et al. 2004). RRF has also been postulated as the main reason for the early survival advantage seen in PD patients compared to HD patients, especially in non-diabetics (van den Wall Bake et al. 2006).

The minimum recommended delivered small solute clearance, as measured by the total (peritoneal and renal) Kt/V_{urea} is $\geq$ 1.7/week (NKF-K/DOQI 2006; Blake et al. 2011). Therefore, the more RRF a patient has, the less important the dialysis dose is in contributing to clearance targets. The RRF contribution to urea clearance can be estimated from a 24-hour

urine collection. Take the example of a 70-kg male patient with residual renal urea clearance of 4 ml/min. The total weekly residual Kt/V_{urea} is 0.96 units/week [urea clearance of 40-L (4 ml/min x 1-L/1000 ml x 60 min/hr x 24-hr/d × 7d/wk) divided by total body water (V_{urea}) of 42-L (70-L × 0.6)], and thus contributes 56% of the total target Kt/V_{urea} (0.96/1.7). As a guide, for each 1 ml/min of residual renal clearance, 0.25 is added to the total Kt/V_{urea} for a 70-kg man (van Biesen et al. 2010). Similarly, each 1ml/min of residual renal creatinine clearance adds 10 L/week/1.73m^2 to the total weekly creatinine clearance. Patients with substantial RRF that reach the weekly target for creatinine clearance (≥ 50 – 60 L/week/1.73 m^2) are at risk of Kt/V_{urea} values below the target (Tzamaloukas 1998; NKF K/DOQI 2006). This is due to the differential renal tubular handling of creatinine and urea in advanced renal failure, secreted in the former and reabsorbed in the latter. Therefore, residual renal creatinine clearance overestimates the glomerular filtration rate, while residual renal Kt/V_{urea} underestimates it. As such, RRF should be evaluated by a 24-hour collection and calculation of the mean urea and creatinine clearance should be used.

Observational data from a recent large study of 583 PD patients found that APD was associated with a higher risk of complete RRF loss in the first year of dialysis compared to CAPD (Michels et al. 2011). However, in a 2007 Cochrane Systematic Review, there was no associated difference between PD modality and preservation of RRF (Rabindranath et al. 2007). The PD prescription should aim to preserve RRF by gradually increasing the dialysis dose, accurately targeting ultrafiltration to avoid dehydration, and using the lowest possible dialysate dextrose concentration required to achieve ultrafiltration (Davies 2009). Two randomized clinical trials have suggested that the use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II blockers (ARB) preserve RRF independent of their effects on blood pressure (Li et al. 2003; Suzuki et al. 2004). Prevention of RRF loss also involves the avoidance of potential nephrotoxins (Bargman et al. 2001). National guidelines (Blake et al. 2011; NKF-K/DOQI 2006) recommend the use of ACEI or ARBS in PD patients to preserve RRF, and the use of diuretics to increase urine volume (in patients with ≥ 100 ml urine/day).

29.2.5 Body Surface Area (BSA) and Body Weight

BSA and body weight affect the prescribed PD dose. Weekly creatinine clearance is normalized to 1.73 m^2 of BSA, while urea clearance is normalized to V, total body water or urea distribution space. V is calculated by Watson's formula and expressed in liters (Watson et al. 1980). BSA is

calculated using Du Bois' formula (Du Bois and Du Bois 1916). The relationship between V and BSA is not linear and is affected by the degree of change of body weight and by gender (Tzamaloukas et al. 1998). Comparing these formulas, an increase in body weight in a given patient will produce an increase in V that is disproportionately greater than the increase in the BSA. That is because body weight is weighted more in the Watson formula than the Du Bois formula. The result is that weight gain causes a relatively smaller decrease in normalized creatinine clearance than in Kt/V_{urea}. Achieving clearance and volume targets in larger patients may require higher fill volumes, such as 2.5 or 3-L fills, especially when RRF is lost but may be limited by discomfort. The effect of increasing fill volumes on clearance and patient tolerability will be discussed later in the chapter.

Technique survival in CAPD has been shown to depend mostly on clearances in relation to body size and RRF (Twardowski et al. 2009). In a prospective observational study of 277 CAPD patients, none of the large patients (BSA > 1.9 m^2, weight > 75 kg, BMI > 25 kg/m^2) remained on CAPD for more than 80 months once RRF was lost, mostly because of inadequate clearances or difficulties with volume control (Twardowski et al. 2009). There were no associations between PET D/P creatinine and BSA, PET D/D_0 glucose and BSA, or PET drain volume and body weight. In a retrospective study of 93 PD (CAPD and APD) patients, there was no association between BMI and long-term technique survival (Barone et al. 2010).

29.2.6 Peritonitis

During an acute episode of infectious peritonitis, vasoactive substances cause enhanced perfusion of blood flow and vasodilation of peritoneal capillaries to increase the effective peritoneal surface area. This results in a transient increase in small solute clearance and a reduction in ultrafiltration (i.e. conversion to High transporter status) that is usually reversible within 1 or 2 weeks of starting appropriate antibiotic therapy (Krediet et al. 1987). In order to preserve ultrafiltration in this setting, adjustment to the PD prescription may be needed by using shorter dwell times and/or non-dextrose dialysate solutions, such as icodextrin. Recurrent peritonitis may result in hyperpermeability of the peritoneal membrane and morphological changes, such as, submesothelial fibrosis and angiogenesis (Fusshoeller 2008).

29.2.7 Patient Compliance

The achieved or delivered PD dose may be significantly lower than the prescribed dose due to poor compliance, commonly through omission of

exchanges or shortening of dwell times. The reported prevalence of non-compliant CAPD patients varies between 10 and 40% and in APD patients between 15 and 20% (Rivetti et al. 2002). In a large questionnaire-based study (Blake et al. 2000) of 656 CAPD patients from Canada and the US, the overall noncompliance rate was 13% (defined as missing more than one exchange per week or more than two exchanges per month). The rate of noncompliance was likely underestimated as the survey measured admitted rather than actual noncompliance. On multiple regression analysis, the following characteristics were independent predictors of noncompliance: greater than 4 exchanges per day, black race, being employed, younger age, and the absence of diabetes (Blake et al. 2000). The results of this study highlight the importance of patient lifestyle considerations when considering CAPD prescriptions and avoidance of more than four exchanges per day. Patient compliance with PD has been evaluated by the administration of questionnaires, home visits, teledialysis, or the use of removable memory cards from cycler machines (Juergensen et al. 2004).

In an attempt to minimize the dialysis burden for patients new to PD, one approach would be to incrementally increase the dialysis component of solute clearance as RRF declines. However, this approach requires diligent monitoring of RRF every 2 month as previously suggested (NKF-K/DOQI 2006). In a study using urea kinetic modeling targeting a weekly Kt/V_{urea} of 2.0, an average sized patient with High-average transport characteristics and RRF can be initiated and maintained for approximately 8-months with a single 2.5-L nocturnal exchange and for 8 to 17 months with two nocturnal exchanges of 2.5 L each (Keshaviah et al. 1994). Another alternative to improving compliance is the use of larger volume exchanges instead of increasing the number of exchanges per day to increase clearance (discussed in the next section). In parts of the world where the cost of dialysis is incurred by patients, this may also affect PD compliance and hence achievable dose of PD.

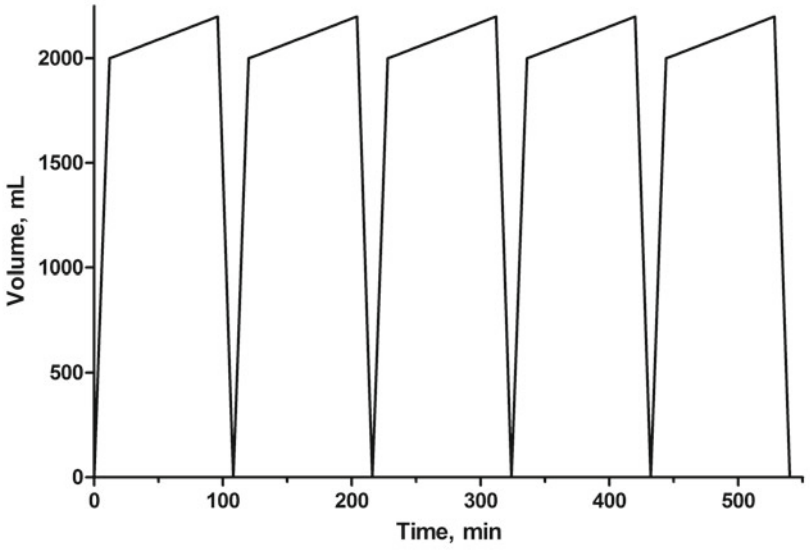
29.3 PRESCRIPTION SPECIFIC FACTORS AFFECTING CHRONIC PD DOSE

29.3.1 APD and Cycle Frequency

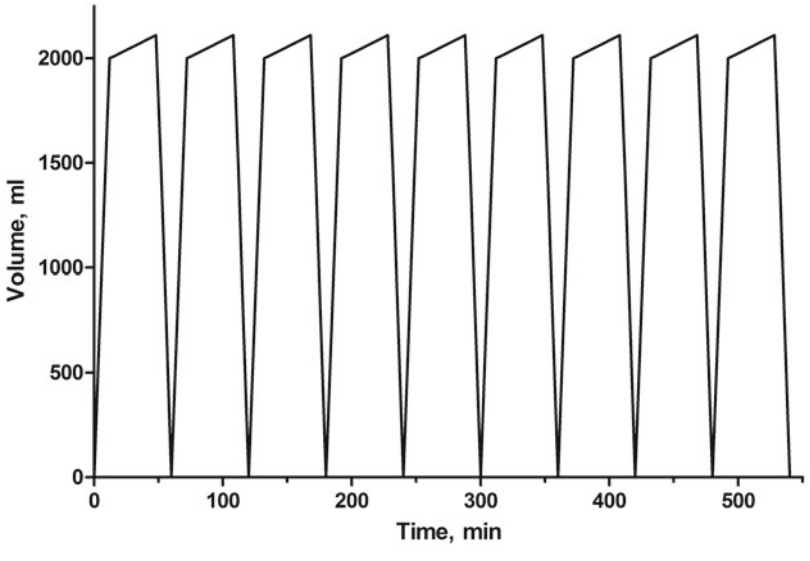
Overnight cycles using an automated device have been used now for decades (Diaz-Buxo et al. 1981; Diaz-Buxo et al. 1984). APD refers to any

type of PD therapy involving an automated device (Kathuria and Twardowski 2009). APD therefore includes: intermittent PD (IPD) whereby patients received 12-24-hours of therapy several times (but not every day) a week, continuous cyclic PD (CCPD) whereby patients perform cycles at night and a long daytime exchange during the daytime, nocturnal intermittent PD (NIPD) which is essentially CCPD without a daytime exchange, and tidal (TPD) which is discussed in more detail below. All of these involve a number of cycles, generally through the night for patient convenience. Another form of APD is continuous flow PD, which has been evaluated as a method to increase solute clearance through the continuous flow of dialysate in and out of the peritoneal space (Diaz-Buxo 2004). It is discussed in more detail later in the setting of acute kidney injury (AKI).

A number of studies have attempted to determine what the optimum number of cycles are in a given time period. Recognizing that with each cycle, time is required to drain and fill, it stands to reason that at some point there is a trade-off where increasing the number of cycles in a given period of time will lead to diminished solute clearance as the drain and fill times becomes an ever-increasing proportion of each cycle and the total dialysis time. Figure 29.2 illustrates this point. A simple analysis of the volume × time product in the different scenarios demonstrates that with increasing frequencies of exchanges, longer fill/drain times have an increasingly negative effect on the total dialysate volume available to the peritoneal membrane (see Fig. 29.3). These examples assume a total therapy time of 9.0-hours, an overall ultrafiltration of 1.2-L for all scenarios, fill volumes of 2.0-L, and varying combined fill and drain time. With increasing number of cycles, the detrimental effect of increasing the drain and fill time is more pronounced. This of course ignores the fact that small solute clearance is not linear and will decrease over the length of an exchange as the concentration gradient dissipates, depending on a number of factors (i.e. fill volume, gradient, solute properties, peritoneal membrane transport properties etc.), but nevertheless illustrates the point and is likely very relevant when considering middle molecule clearance, as is discussed later.

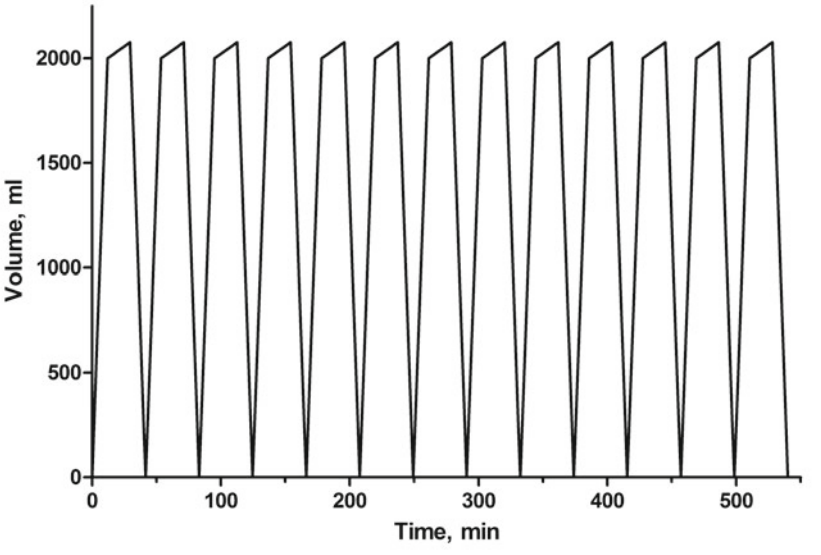


(a)



(b)

Fig. 29.2 Nightly intermittent PD over 9 hours showing three scenarios with 2.0-L fill volumes: (a) 5 exchanges; (b) 9 exchanges; and (c) 13 exchanges.



(c)

Fig. 29.2 (Continued)

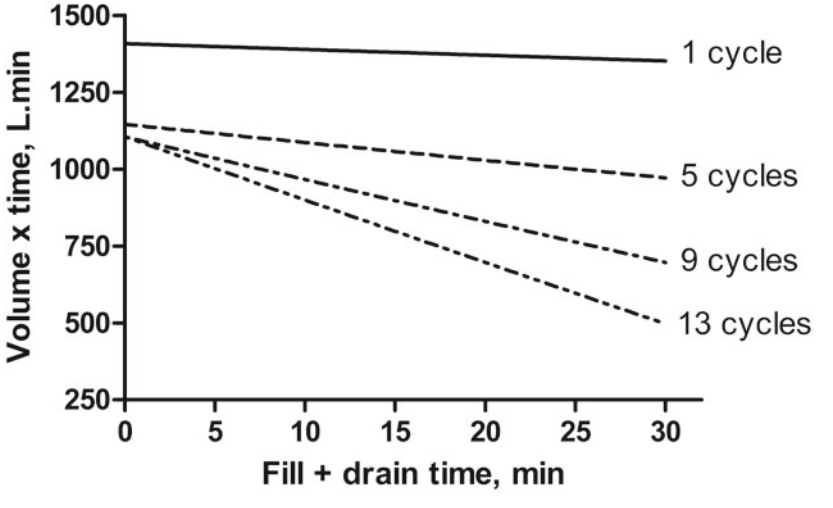


Fig. 29.3 The calculated product of *volume x time* in 9 hours of nightly intermittent PD based on varying number of exchanges (1, 5, 9, and 13) of 2.0-L and fill and drain times for each exchange. The calculations assumed a net ultrafiltration for all scenarios of 1.2-L.

How long does the fill and drain phases take? Brandes et al found that fill rate was faster for a greater fill height and for patients in the supine position (Brandes et al. 1995). Larger bore catheters did not influence the findings. The average fill rate was 290 ml/min and was completed after 7.9 minutes. The drain phase was characterized by an initial rapid and linear rate of 350 ml/min achieving 83% of the fluid removal after about 5 minutes. This was followed by a transition phase and a subsequent much slower drain rate (36 ml/min), presumably due to the viscera collapsing on the catheter at the transition point. Not surprisingly, the time to the transition point was shortened by an increased drain height. These results suggest that the drain time could be shortened without leaving much fluid behind and thereby increasing clearances by lengthening the dwell times.

Baczynski and colleagues conducted a study in 17 PD patients to determine the impact of drain and fill periods of a cycle on solute removal (Baczyski et al. 2010). Briefly, they carried out an infusion of dialysate followed immediately by drainage; the time taken was noted and a sample drawn to determine the solute mass removal (concentration × volume) during the first experiment. In the second experiment, an exchange with the same dialysate volume was then performed for the same duration as in the first dwell. The fluid was then again removed and a sample drawn. This is shown schematically in Fig. 29.4. The PD efficacy of the infusion and drainage period was calculated as the ratio of the solute removal in the first experiment to that of the second experiment, less correction made to subtract the additional impact of an infusion and drainage period in the second experiment. The authors took into account the residual volume present in each experiment, which was assumed to be 222-ml based on previous experiments by the research group. This value is likely to vary between patients in reality and may introduce some error in the calculations. They also adjusted for the time-dependency of solute removal – i.e. there will be less solute removal during the drain phase in the second experiment because of the preceding dwell, lessening the concentration gradient across the peritoneal membrane. This 'correction factor' was based on previously determined isotope experiments and estimated to be 0.89 for urea and 0.90 for creatinine. Thus for determination of the efficacy of urea removal during the inflow and drain phases, the final equation would be:

$$k = \frac{C_1 V_1}{C_2 \left(V_2 + 222 \right) - 222 C_1 - 0.89 C_1 V_1} \tag{29.5}$$

where C_1 and C_2 represent the solute concentrations (urea or creatinine) of the drawn samples in the two experiments and V_1 and V_2 the respective volumes of dialysate upon drainage. The overall estimate of k was 0.87 for urea and 0.68 for creatinine, however several patients had values greater than unity, bringing into question the validity of such a method. An alternative, more pragmatic approach is to use a value of 0.5, assuming that on average half of the dialysate volume is available to the peritoneal membrane during the inflow or drain period (Amici 1998).

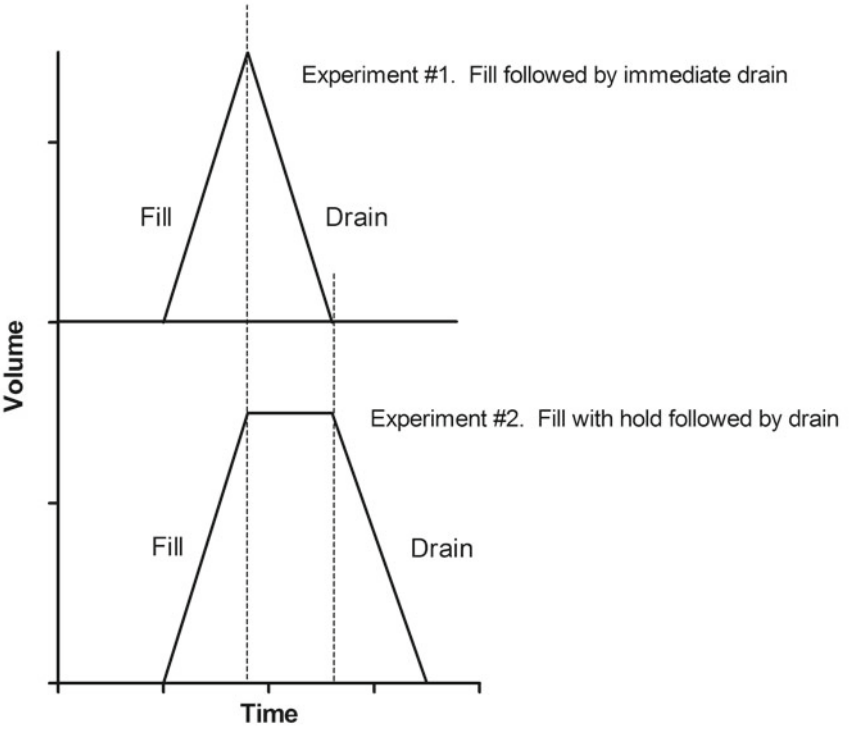


Fig. 29.4 An illustration of the experiment conducted by Baczyski et al. 2010 designed to determine solute clearance restricted to the fill and drain phases of an exchange. The upper panel shows fluid is infused followed immediately by drainage of the fluid. In the lower panel fluid is held after the initial infusion for the same period of time as the drain phase determined from the first experiment. Fluid is then drained out.

Juergensen and colleagues (Juergensen et al. 2002) examined the effects of increasing the exchange frequency (and therefore total volume) in 11 APD patients over a fixed time period of 9-hours. Patients had fill volumes of 2.5-L during the cycles with a final volume of 2.0-L to hold during the

day. They used convenient total volumes of 9.5-L (3 cycles), 14.5-L (5 cycles), and 19.5-L (7 cycles) to make use of 2, 3, or 4 × 5-L dialysate bags. Each participant performed each of the schedules one week apart. The authors found, not unexpectedly, that peritoneal clearance, as measured by either pKt/V_{urea} or peritoneal creatinine clearance, increased with increasing cycle frequency (to a maximum of seven). The pKt/V_{urea} increased from 1.68 in the 9.5-L trial to 2.06 in the 14.5-L and 2.29 in the 19.5L trials, respectively. This increase of 23% and 36% in the 14.5-L and 19.5-L trials was greater than the 16% and 21% increases observed for the creatinine clearance. The increase in clearances observed was accompanied by increases in ultrafiltration, more so in the Low-Average transporters compared to the High-Average and High transporters.

29.3.2 CAPD and Exchange Frequency

Similarly to APD, one would expect that an increase in exchange frequency in CAPD would lead to increased clearance of small solutes. This is at the expense of increased costs and possible decreased quality of life due to the increased time involved in performing the exchanges during the daytime. Szeto and colleagues evaluated 100 anuric CAPD patients who were stable but required an increased intensity of dialysis using a non-randomized design (Szeto et al., 2002). Fifty agreeable participants added an additional 2.0-L exchange (baseline 3 or 4 exchanges) while an additional 50 participants who did not agree to the increase represented the control group. A significant increase in Kt/V_{urea} of 21% was observed in the intervention group (1.58 to 1.91); no change was seen in the control group. A similar increase was observed with creatinine clearance. Ultrafiltration volume increased 210 ml with the increase in the number of exchanges.

29.3.3 Fill Volumes in CAPD and APD

As has been previously pointed out, peritoneal clearance of small solutes such as urea are determined solely by dialysate flow rate once equilibrium has been achieved between the plasma and dialysate. To enhance dialysate flow rate, i.e. drain volume, the options include increasing the fill volumes, increasing the number of exchanges, or enhancing ultrafiltration by increasing the osmotic strength of the dialysate (Krediet et al. 1998). From a patient's perspective it would seem likely that an increase in the fill volume, if not associated with adverse symptoms, would be preferable to an additional exchange which is time-consuming and may impact on quality of life.

The traditional peritoneal dialysate volume (fill volume) used in patients is 2.0-L. Increasing the fill volumes with each exchange should increase solute removal by increasing dialysate flow rate, but as already mentioned, at the expense of additional fluid used and potential side-effects including patient discomfort, the development of hernias etc. Keshaviah and colleagues carried out a study to determine the relationship between BSA, fill volume and solute removal in PD patients (Keshaviah et al. 1994). They found that the K_oA (overall membrane permeability × surface area) increased in a linear fashion between 0.5 and 2.0-L fill volumes with a near-doubling over this range. Diminishing returns were observed however as the fill volume was increased to 3-L with less than a 10% further increase in the K_oA. However, the peak K_oA increased with BSA, suggesting that fill volumes can be increased with larger patients. The explanation for the effect of fill volume on K_oA is that it recruits a greater amount of the peritoneal membrane surface area. Even higher volumes appeared to decrease the K_oA, suggesting that at these volumes complete mixing of the dialysate does not occur.

A more recent study further clarified the effects of increased fill volume as previously mentioned. Ten PD patients underwent two separate studies of a 2.0-L and 3.0-L dwell. Each 1.0-L of solution contained 790-ml of 1.36% glucose-based solution, 160-ml of 0.45% NaCl, 50-ml of CT-contrast, and radio-labeled albumin to estimate peritoneal volume (Chagnac et al. 2002). CT-imaging of the peritoneal space was undertaken to estimate peritoneal surface area in contact with the PD solution. The authors found that increasing the dialysate volume from 2-L to 3-L (resulting increased volume 46%) led to an 18% increase in effective peritoneal surface area (0.57 to 0.67 m^2).

Previous modeling studies suggest that for the typical CAPD on 2.0-L × 4 exchanges, in the absence of RRF, a significant proportion of patients would not be able to achieve a total weekly Kt/V_{urea} of 1.7 (Nolph et al. 1994). Low/Low-average transports more than 67 kg would likely have weekly Kt/V_{urea} values less than this while High-average and High transporters above 63- and 61-kg respectively, would also be receiving insufficient dialysis based on this criterion. In the absence of peritoneal function testing, another study suggested that 90% of CAPD patients receiving a drain volume:total body volume ratio of at least 0.304 would have a pKt/V_{urea} of at least 1.7 (Tzamaloukas et al. 2007). As an example, a 70-kg patient with an estimated volume of 40.6-L would need to have a drain volume of 12.3-L, an improbable value in CAPD patients. Such a drain volume would be difficult to achieve without some combination of 3.0-L fill volumes, increased number of exchanges, and/or high ultrafiltration rates.

The average weight in the validation cohort was 69.3-kg and the average drain volume 9.0-L as a point of comparison. This would confirm the suggestion that standard CAPD 2.0-L × 4 exchanges in insufficient in the majority of CAPD patients based on clinical practice guidelines, particularly in the absence of significant RRF.

While there is no question that increasing fill volumes will increase small solute clearance, tolerability must be assessed. This question has been addressed in several studies. A small study of 11 patients sought to determine whether 2.5-L exchanges could be tolerated in a CAPD regimen (George et al. 1989). Eight of the patients substituted all 4 of their 2.0-L exchanges while the remaining 3 patients substituted 1 exchange. In the 8 patients who substituted all exchanges for the larger volume, the daily urea clearance increased 14.6% and the creatinine clearance 9.5%. No change in the ultrafiltration was observed although a trend to increased ultrafiltration in the 2.5-L fill volume group was observed. More modest changes were seen in the remaining three patients. Importantly, the vast majority of patients tolerated the increased volumes without worsening symptoms – 10 of the 11 patients would continue the 2.5-L fill volumes.

Harty et al. conducted a randomized controlled trial in CAPD patients in which patients already on a 2.0-L × 4 exchange prescription were randomized in a 2:1 fashion to receive an increase in fill volume of 0.5-L or to maintain the same prescription (Harty et al. 1997). The primary outcome was urea and creatinine clearance at 1-year. As a result, 42 patients were randomized to the increased volume and 26 patients to maintain current volumes. Unfortunately, 28 patients failed to complete the 1-year follow-up (transplant, transfer to HD, medical illness, and death) and 7 patients in the increased fill volumes group were intolerant to the change in regimen (29%). Not surprisingly, patients who were intolerant had lower body weight and BSA and were more likely to be women, reflecting the smaller size of the female patients. Of the remaining 17 patients who tolerated the increased volumes, daily drain volume increased from 8.9-L to 10.7-L at 1-year ($P< 0.0001$) and pKt/V_{urea} increased from 1.59 to 1.78 (12% increase, $P=0.0005$). RRF declined at a similar rate in those who were tolerant to the prescription change and the control group. While these findings suggest that increasing fill volumes can increase drain volume and small solute clearance, they also point to the fact that larger volumes are often poorly tolerated.

Harris and colleagues randomized 12 CAPD patients in a double-blind cross-over design to either 2.0, 2.5, or 3.0-L exchanges (Harris et al. 2001). Intra-peritoneal pressure was measured and the McGill pain questionnaire

administered to assess tolerability. With the larger volumes there was a tendency to increased discomfort based on only one of the sub-domains. Intra-peritoneal pressure increased with the larger volumes immediately post infusion but tended to drift back towards baseline after 3-hours into the exchange. It should be noted that only a 1.36% glucose-based fluid was used. Presumably higher strength dialysate would lead to greater ultrafiltration and drain volume and a greater potential for discomfort due to increased intra-peritoneal pressures.

A multi-centered study of 81 CAPD participants was carried out to determine the resulting intra-peritoneal pressure and subjective discomfort of increasing fill volume from 2.0 to 2.5 and 3-L (M de Jesus et al. 2000). Participants were blinded to the fill volumes to prevent bias. Not surprisingly there was an increase in intra-peritoneal pressure with increasing fill volumes; this was associated with a small but statistically significant increase in diastolic blood pressure. More importantly, subjective discomfort was higher for the larger volumes, however, 44% of participants had a low discomfort score with 3.0-L fill volumes compared to 86% of participants with 2.0-L and 64% of participants with 2.5-L volumes. The authors did not find any relationship between intra-peritoneal pressure and subjective discomfort. Intra-peritoneal pressure may be a more useful measure in children. In one small study of five children, initial fill volume of 940 ml/m^2 was titrated upwards based on intraperitoneal pressure measurements (Fischbach et al. 1997). As a result of this, the fill volume was increased to 1230 ml/m^2 and weekly Kt/V_{urea} increased from 1.61 to 2.03.

Twardowski and colleagues have shown that increasing fill volume to 3.0-L is tolerated in about 50% of patients – those who did not tolerate this increase had dramatic decreases in forced vital capacity and forced expiratory volume particularly in the supine position (Twardowski et al. 1983).

A different approach was taken in a recent study to assess the impact of higher fill volumes on patient tolerance (Davis et al. 2011). The authors searched the Manufacturer and User Facility Device Experience (MAUDE) database to investigate events reported related to “overfilling”. Overfill, as the authors point out, was a term historically used by manufacturers to describe an event when an excessive amount of fluid infusion takes place, either due to machine malfunction or user error, leading to an increase in intraperitoneal volume. Overfill can also occur as a result of excessive ultrafiltration or because of inadequate drainage of intraperitoneal fluid prior to the next fill. The authors identified such complaints and related the severity of the event (minor, moderate, major, or death) to the ratio of the drain volume to fill volume (DV/FV). A significant

relationship was observed with higher ratios observed in the more serious cases. There were ten reports of major complaints with an associated DV/FV ratio of 2.14, as compared to 1.63 for minor cases. Insufficient drain associated with subsequent infusion was the presumed cause of 88% of cases.

Patient discomfort may not be the only drawback to increased fill volumes. One study has demonstrated that there is a significant decrease in cardiac output, measured non-invasively, with an accompanying decrease in stroke volume and increase in total peripheral resistance as the dialysate volume was increased from 2.0-L to 3.0-L (Ivarsen et al. 2007). This was hypothesized to be due to decreased venous return from the increased intra-abdominal pressure. Additionally, there has been evidence to suggest that increased fill volumes (i.e. 3.0-L) are associated with increased appearance of inflammatory markers such as TNF-α without increased removal of middle molecules such as ß2-microglobulin (Paniagua et al. 2004).

A small study of 8 CAPD patients with inadequate solute removal or ultrafiltration using a standard 2.0-L × 4 exchange regimen underwent two separate experiments of a 4-hour dwell with either 2.0-L or 3.0-L of dialysate. The mass transfer of small solutes such as urea and creatinine increased about 40% without a similar increase in the MTAC, suggesting that the higher volumes increased solute removal primarily by increasing the dialysate flow rate and therefore the transperitoneal concentration gradient rather than by increasing the effective surface area (Krediet et al. 1988). These results are not necessarily different from that of Keshaviah's group who observed minimal increases in the K_oA beyond 2.0-L (but substantial increases up to 2.0-L). The increased volume did not affect ß2-microglobulin removal, consistent with previous observations that middle molecule clearance is more a function of total contact time with the peritoneal membrane surface as is discussed later. The study was limited by the small sample size and multiple comparisons. Of some concern, the ultrafiltration volume decreased in the 3.0-L versus 2.0-L fills, presumably due to increased lymphatic absorption from the higher intra-abdominal pressures. As the authors point out in a subsequent review, higher glucose strength solutions may offset the increased lymphatic absorption by the increased transcapillary ultrafiltration.

The largest study to address the issue of increased fill volumes was the ADEMEX study (Paniagua et al. 2002). CAPD patients were randomized to continue 2.0-L × 4 exchanges or to an intensified PD regimen to achieve a target peritoneal creatinine clearance of 60 L/week/1.73 m^2. This enhanced clearance was achieved as follows. Patients with a BSA of ≤ 1.78 m^2

received a prescription of 2.5-L × 4 exchanges while those patients with a BSA > than 1.78 m^2 received 3.0-L × 4 exchanges. Patients who failed to reach the clearance target but tolerated the increased volume received a fifth exchange through the night. Patients who achieved the peritoneal creatinine clearance but were intolerant of the increased fill volumes underwent a combination of 2.5 (daytime) and 3.0-L (overnight) exchanges. Ultimately, only 85 patients required a fifth exchange indicating that this study was primarily an intervention of increased fill volumes. Total daily dialysate volume was 10.0-L for 37% of patients, ranging up to 15.0-L for 14% of patients. The peritoneal creatinine clearance increased from 44.5 to 57.0-L/week/1.73 m^2 and the pKt/V_{urea} from 1.59 to 2.13 (Paniagua et al. 2005). It is difficult to know however, specifically what the relationship was between increased fill volumes and enhanced clearances due to the lack of information about patient-specific interventions and associated increased clearances. A 100-ml/day increase in ultrafiltration was also observed with the increased fill volumes.

29.3.4 Increasing Ultrafiltration

A number of studies have examined the impact of ultrafiltration on clinical outcomes. The data comes primarily from observational studies, which demonstrate at least a trend to increased mortality with smaller ultrafiltration volumes (Ates et al. 2001; Brown et al. 2001; Jansen et al. 2005). This type of data can be confounded by RRF (although NECOSAD was a study of anuric patients), membrane transport status, salt and fluid intake, and middle molecule clearance. Increasing ultrafiltration, through the use of dialysis fluid with higher strength of glucose or the use of an icodextrin-based solution, should increase the removal of solutes of varying sizes via convective clearance. Most studies have evaluated the role of these solutions as a means to increase ultrafiltration rather than clearance however. A recent meta-analysis and systematic review identified five randomized controlled trials comparing urea and creatinine clearance using icodextrin or a glucose-based solution for an overnight dwell (Qi et al. 2011). Peritoneal creatinine clearance ranged between 2.59 and 4.4 with a weight mean difference of 0.51 compared to glucose. Similar results were seen with urea. Results were highly significant for both solutes and heterogeneity in the studies was not observed. This meta-analysis confirms the clinical impression that enhanced ultrafiltration with icodextrin will increase small solute clearance, presumably through increased convective clearance. While increasing the glucose strength of dialysis solutions will presumably also increase clearance through increased convective clearance, the increased glucose exposure may have long-term detrimental effects on the

patient and is therefore not a recommended strategy to increase solute clearance (Blake et al. 2011).

29.3.5 Tidal PD

TPD is a method that has been around for decades (Steinhauer et al. 1991). The basic concept is that rather than exchanging the entire drain volume only a portion of it is removed with a similar amount re-infused in order to maintain dialysate contact with the peritoneal membrane. While advantageous in patients who have pain with outflow of the dialysate where typically a small portion of the fluid is left in with each exchange, its role to enhance clearances has not been shown to be as useful. Additional, as discussed below, TPD may also have a role in patients who have prolonged drain profiles.

One of the earliest studies to promote the usefulness of TPD was that of Flanigan et al (Flanigan et al. 1992). Using an automated device, 30 to 50 ml/kg of dialysate was infused and left to dwell. Subsequently, a tidal drain volume was removed (tidal inflow + weight gain/number of exchanges), the remaining volume is called the reserved volume. Fresh dialysate was then infused (typically 10 to 25 ml/kg) and the process is repeated for the required number of cycles. The hope is that the trade-off between decreased solute clearance because of equilibration of the reserve volume would offset the decreased clearance that occurs during the fill and drain phases of the cycle. In this particular study, APD consisted of 10-hours of overnight therapy (4-5 x 40-mL/kg exchanges) plus a daytime dwell of 20 mL/kg. Patients were then converted to TPD using 8-hours overnight with an initial fill volume of 40 mL/kg and tidal exchanges of 10 to 20 mL/kg to provide hourly dialysate flows of 25 to 70 mL/kg/hr. Hourly dialysate flows were increased incrementally to achieve urea removal equal to that observed with APD. Although TPD delivered enhanced urea removal, 16.0-L vs. 9.5-L used in APD was required.

Another study took CAPD patients through a series of prescription changes to evaluate solute clearance (Rodriguez et al. 1998). Patients went from CAPD to APD (average overnight volume 14.3-L, exchange volume 2.4-L, daytime volume 1.9-L), 50% TPD (matched to the APD regimen but exchanges reduced from 59.3-minutes to 37.8-minutes), and 25% TPD (exchange 19-minutes). Kt/V_{urea} increased in APD compared to CAPD (2.03 vs. 1.51) while TPD was intermediate (1.88 with 50% TPD and 1.80 with 25% TPD. Another smaller study found similar clearances of urea and creatinine between intermittent PD and 50% TPD when dialysate flow rates were matched (Piraino et al. 1994).

Juergensen and colleagues carefully studied varying TPD prescriptions compared to conventional APD (Juergensen et al. 2000). One group of patients received a total of 15.0-L dialysate over 9.5-hours with the tidal volume varied between 10%, 25%, and 50%. A second group of patients received 24.0-L of dialysate over the same time period using 25% and 50% tidal volumes. In the 15.0-L group, the 10% and 25% tidal volumes achieved significantly less Kt/V_{urea} than the 50% TPD and APD regimens. No differences in peritoneal creatinine clearance were observed. No differences were observed in the 24.0-L group although there was a trend to increased creatinine clearance in the 50% tidal volume and APD regimens.

Finally, one study compared APD to TPD in 30 patients using both one APD and one TPD treatment session using the same overnight duration (9 hours), total treatment volume (15.0-L), and fill volume (2.5-L) (Vychytil et al. 1999). A tidal volume of 50% was used. The authors found that urea clearance was modestly higher during APD than TPD (0.52 vs 0.49). When patients were sub-divided into Low/Low-average and High/High-average groups, only the lower transport group demonstrated enhanced clearance in the APD group.

Finally, Gotch using mathematical modeling examined the impact of varying drain/fill times on the efficiency of APD compared to TPD. His analyses suggested that patients with prolonged fill/drain periods would receive enhanced clearance with TPD whereas patients with typical fill/drain profiles would be better served continuing with traditional APD unless the dialysis flow rate exceeds 2 L/hr (Gotch 2002).

29.3.6 Miscellaneous Scenarios in APD

A number of options could be considered in APD patients when the dose is to be increased in order to achieve target. Two different scenarios are considered below. Demetriou and colleagues carried out a study that asked whether the addition of a manual exchange versus increasing the nightly dialysate flow volume was the best strategy to increase clearance in APD patients (Demetriou et al. 2006). The study design was a randomized crossover of 22 Low-average or High-average patients comparing 1 week of each of the following 2 strategies. In the manual daytime exchange intervention, patients performed 5 exchanges of 2.0-3.0-L (based on BSA) overnight over 9 hours with a 10-hour last fill of 2.0-L icodextrin, followed by a subsequent manual exchange of 2.0-2.5-L for the last 5-hours before the next cycle. Somewhat unusually, 75% tidal volumes were used rather than standard APD exchanges overnight. In the high-flow arm, patients again performed APD over 9 hours using variable volumes and 75%

tidal volumes, this time however with 13 exchanges. Participants then had a last fill of 2.0-L icodextrin until the next evening (15-hours). Eighteen patients completed the study and were included in the analyses. High-flow treatment was associated with a modest but significant increase in urea clearance (12.83 vs. 11.68-L) and creatinine clearance (12.83 vs. 11.68-L), however no difference was observed with phosphate clearance, ultrafiltration, and ß2-microglobulin clearance. Of concern, sodium removal was decreased in the high flow group (128.0 mmol/day vs. 176.4 mmol/day). This finding was almost certainly due to the sodium sieving that takes place with such short dwell times. Also a major concern was the estimation of a 34.3%-59.4% increased cost associated with the high-flow strategy. The rationale for using a 75% tidal volume was not clearly identified and the possibility that use of standard APD may have modified these results must be acknowledged.

Another important, albeit small study, measured urea and creatinine clearance in 8 patients using the following four APD prescriptions: 5 × 2.0-L, 7 × 2.0-L, 9 × 2.0-L, and 50% TPD, 14.0-L (Perez et al. 2000). All prescriptions occurred over 9-hours. Urea clearance increased from 7.5 to 8.6 and 9.1-L/night with the increasing number of exchanges. Creatinine clearance increased in a similar fashion. The TPD strategy was only superior in clearance to the 5-exchange prescription with a urea clearance of 8.3-L/night. Unlike the aforementioned study by Demetriou (Demetriou et al. 2006), sodium removal was enhanced with the increasing number of exchanges (114.9 mmol/night with 5 exchanges and 194.2 mmol/night with 9 exchanges). Patients with Low or Low-average transport status tended to have more modest benefits from the increased exchanges.

29.3.7 Middle Molecule Clearance

A large body of knowledge exists on the relationship between so-called middle molecules and their role as uremic toxins. A detailed discussion of this role is beyond the scope of this chapter. What is relevant, however, is the impact of different PD treatment strategies on middle molecule clearance. Clearance of middle molecules does not appear to simply follow from that of the smaller solutes such as urea.

It has been previously suggested that PD was associated with greater middle molecule clearance than with HD due to the high peritoneal membrane permeability, continuous mode of therapy, and better preservation of RRF (Keshaviah 1993). The latter is not only associated with enhanced clearance of middle molecules through convective clearance, but tubular metabolism and secretion as well (Evenepoel et al. 2006). A more recent

study compared high-flux HD to CAPD and APD found that HD was associated with greater clearance of ß2-microglobulin and p-cresol, a protein-bound toxin (Evenepoel et al. 2006). However, clearance of both of these molecules was greater in CAPD than APD, although the differences did not reach statistical significance due to the small sample size. An older study demonstrated that removal of ß2-microglobulin in CAPD patients was linear for up to 400 minutes, consistent with the notion that increasing the number of exchanges is not beneficial but rather duration of contact with the peritoneal membrane (Lysaght et al. 1989). This is further supported by the observation that CAPD patients tended to have higher clearances of ß2-microglobulin with two exchanges compared to three or four exchanges per day over twenty-four hours (Kim et al. 2001).

Finally, the use of icodextrin to enhance ultrafiltration has also been shown to be associated with enhanced clearance of middle molecules as compared to either 1.36% or 3.86% glucose-based dialysate (Ho-dac-Pannekeet et al. 1996). These and other studies suggest that middle molecule removal in PD is achieved through prolonged contact with the peritoneal membrane and amount of ultrafiltration achieved. Whether this is clinically important is less clear and requires further study.

29.4 FACTORS AFFECTING PERITONEAL DIALYSIS DOSE FOR THE TREATMENT OF ACUTE KIDNEY INJURY

The use of PD and factors affecting dosing in the treatment of AKI warrants special consideration. There is no consensus on the best dialysis method or dose in AKI and both hemodialysis (HD) and PD are used (Gabriel et al. 2008; Burdmann and Chakravarthi 2011). In the 1970s, PD gained widespread popularity in the treatment of AKI (Ash and Bever 1995; Steiner 1989). The only prerequisite for performing PD was an intact peritoneal cavity and access could be established promptly and safely by the insertion of a semi-rigid catheter at the bedside. With the availability of a flexible single cuff Tenckhoff catheter and automated cycler in the 1980s, studies reported positive results compared to intermittent HD in electrolyte and metabolic control (Sipkins and Kjellstrand 1981). However, with the increasing popularity of continuous (extracorporeal) renal replacement therapy (CRRT) since the late 1990s, PD has fallen out of favor (Hyman and Mendelssohn 2002; Rao et al. 2003). In a large international prospective observational study (Uchino et al. 2005) of AKI patients in the intensive care units at 54 centers in 23 countries, 73% of the 1738 enrolled patients were treated with dialysis. CRRT was used most often (80%), followed by intermittent HD (17%), compared to approximately 3%

treated with PD. Nonetheless, acute PD remains the mainstay of dialysis therapy in pediatrics and in adults in developing countries due to its ease of administration, availability, technical simplicity, large volume removal with hemodynamic tolerability, gradual correction of acid-base and electrolyte imbalance, and lack of need for anticoagulation (Ansari 2011; Alarabi et al. 1994; Gabriel et al. 2006; Reznik et al. 1991).

29.4.1 PD Dose and Adequacy Considerations in AKI

The adequacy of dialysis dose in AKI is the subject of controversy as there are no satisfactory markers of adequacy or consensus on what rate of urea solute removal is adequate or optimal (Claure-Del Granado and Mehta 2011; Paganini 1998). Urea kinetic modeling has been applied to patients with AKI, although, it has not been validated for use in the critically ill population (Schiffl 2007; Claure-Del Granado and Mehta 2011). There are several limitations to the extrapolation of the clearance-based dialysis dosage, such as Kt/V_{urea} and creatinine clearance from the chronic dialysis population for use in AKI. Firstly, patients with AKI are often in a hypercatabolic state. Urea generation can vary on a hourly basis requiring a dynamic urea kinetic model (Chitalia et al. 2002). Secondly, the calculation of the volume of distribution of urea (V_{urea}) using derivative formulae has been shown to consistently underestimate the true V_{urea} due to excessive production of endogenous water in AKI (Himmelfarb et al. 2002). Furthermore, there are neither randomized studies comparing various doses of PD and its effect on clinical outcomes in AKI; nor are there clinical guidelines on a minimum target dose of PD in AKI (Evanson et al. 1998; Paganini 1998; Claure-Del Granado and Mehta 2011). Extrapolating data from HD studies in AKI, a minimum weekly dose of standard Kt/V_{urea} of 2.1 has been suggested with even higher small solute targets in highly catabolic patients (Chionh et al. 2010).

The clearance of MMW molecules, such as, pro-inflammatory cytokines, with the goal to attenuate the inflammatory response has been a treatment target in sepsis-associated AKI but currently there are no established method and clinical evidence for dosing PD based on MMW clearance (Ronco et al. 2008; Chionh et al. 2010). Clearance of small urea and MMW molecules in AKI, however, may not be the major determinants of short-term outcomes, but rather the adequate removal of “very small waste” (i.e. potassium, hydrogen ions, etc.) and fluid overload (Claure-Del Granado and Mehta 2011). However, these parameters have not been the target of dialysis adequacy measurements in randomized dialysis dose studies. Persistent hypervolemia in critically ill patients have been associated

with adverse clinical outcomes, including, mortality, prolonged ventilation, AKI and increased length of intensive care stay (Bagshaw et al. 2008; Cerda et al. 2010; Yerram et al. 2010). The use of PD in AKI adequately accomplishes volume removal and is well tolerated in hemodynamically unstable patients (Chitalia et al. 2002; Gabriel et al. 2007). One limiting factor with the use of PD in AKI is the control of ultrafiltration volume due to a combination of inability to accurately monitor intraperitoneal volumes and variability in ultrafiltration with fixed dextrose exchanges (Chionh et al. 2010). Although the same situation applies in patients on chronic PD, the requirement in the intensive care setting for higher fluid intakes coupled with more rapid changes in clinical status makes the use of PD a challenge in AKI requiring experienced staff.

Hypercatabolism is often found in patients with rhabdomyolysis, multiorgan failure, and sepsis. Given the slow continuous solute removal with PD, the efficiency of PD to treat uremia in hypercatabolic patients has been the subject of controversy (Mehta and Letteri 1999; Steiner 1989; Phu et al. 2002). Several studies have reported positive outcomes associated with PD in hypercatabolic patients (Bohorques et al. 1990; Chitalia et al. 2002; Gabriel et al. 2006, 2007; Gastaldi et al. 1981; Indraprasit et al. 1988). However, these studies are limited by small sample size, inconsistent definition of hypercatabolism, inappropriate or lack of measurements for catabolic state, and variable definitions of PD success (Ansari 2011).

29.4.2 PD Prescription Factors Affecting Dose

Similar to in chronic PD, the key determinants of solute clearance in AKI are dialysate flow rate, effective peritoneal surface area, BSA/body weight, and RRF (Chitalia et al. 2002; Gabriel et al. 2008). The acute PD dialysis session length can vary significantly (12 to 72 hours) depending on the etiology and duration of AKI, the amount of solute and fluid removal required, and the need for ongoing nutritional support (Passadakis and Oreopoulos 2007). Acute PD prescriptions should be reassessed every 24 hours in acutely ill patients to see if changes need to be made to meet catabolic demands, solute and fluid targets. Dextrose based solutions play a key role in acute PD; other solutions such as amino acid and icodextrin have little utility in this setting. With a standard regimen, using 2.0-L hourly exchanges with 1.5% dextrose results in an ultrafiltration rate of 50 -150 ml/hour (1200 – 3600 ml/24 hour). The use of higher tonicity dextrose solutions, 2.5% – 4.25% can result in large volume fluid removal of 200 – 400 ml/hour (Passadakis and Oreopoulos 2003).

29.4.3 PD Techniques in AKI

29.4.3.1 Intermittent PD

Classical Intermittent PD (IPD) is the oldest PD modality and has been used widely in the treatment of AKI (Cameron et al. 1967; Tzamaloukas et al. 1973). A typical acute IPD session is 16-24 hours long, with each session comprising 20-30 exchanges of 1- 3-L of dialysate every hour (Passadakis and Oreopoulos 2007; Burdmann and Chakravarthi 2011). The delivered doses with IPD typically vary from 40 to 60-L per session (urea clearance 8 – 12 ml/min). In a randomized trial (n = 70) comparing acute intermittent PD (IPD) and hemofiltration in a Vietnamese population, in which malaria (69%) was the leading cause of AKI, treatment with IPD was associated with higher mortality, slower decline in creatinine and worse acid-base control (Phu et al. 2002). However, this study has been criticized as the IPD group used rigid catheters, an open system with manual exchanges, and too short a fill time that may have contributed to the poorer outcomes observed (Daugirdas 2002). Adequate small solute clearance may be difficult to achieve with IPD in hypercatabolic patients (Burdmann and Chakravarthi 2011).

29.4.3.2 High-Volume PD

High-volume continuous PD (HVPD) is a modality developed to increase higher small solute clearance. A 24-hour treatment using HVPD (36-44 L/session) can produce as much small solute removal as a 4-hour session of HD (Gabriel et al. 2007). This was demonstrated in a prospective cohort study of 30 AKI patients that used high volume PD (targeting pKt/V_{urea} 0.65 per session), the achieved normalized creatinine clearance and pKt/V_{urea} values were 110 L/week/1.73 m^2 and 3.8 respectively. The same group (Gabriel et al. 2008) followed up with a randomized control trial in 120 patients with AKI secondary to acute tubular necrosis comparing high volume PD with daily HD. The high volume PD session was defined as 24-hours of dialysis with sessions performed 7 days per week using a cycler through a flexible Tenckhoff catheter. Two-liter exchanges were performed with 35 to 50 minute dwell times for a total of 36 to 44-L/day and 18 to 22 exchanges/day. In the daily HD group, a session lasted at least 3-hours and was performed 6 times/week. Baseline characteristics were similar for age, gender, severity of AKI, and APACHE II score, predialysis urea and creatinine. Patients that were highly catabolic, as defined by Schrier's criteria (Schrier 1979) were excluded. Metabolic control, mortality, and renal function recovery were similar in both groups. However,

the reported 30-day mortality was high in both groups (HVPD 58% versus daily HD 53%, P=0.49). The weekly delivered Kt/V_{urea} was lower in the HVPD group (3.6 versus 4.7, P<0.01).

29.4.3.3 Continuous Equilibrated PD

Continuous equilibrated PD (CEPD) is similar to CAPD but more intensive and can be performed manually or with a cycler. Compared to IPD, the dwell times are longer. Dialysate is continuously instilled and drained every 2-6 hours to provide 4 to 8 dwells daily (Bohorques et al. 1990). This technique provides low-flow continuous dialysis that may not be adequate for highly catabolic patients (Ansari 2011). Compared to IPD, CEPD achieves lower solute clearance due to the lower dialysate flow rates (urea clearance 5 – 7 ml/min) (Amerling et al. 2003; Nolph 1988).

29.4.3.4 Tidal PD

TPD is performed with a cycler using rapid exchanges and a constant tidal volume in the peritoneal cavity that is not drained, typically 50% of the initial fill volume (2 to 3-L) (Chitalia et al. 2002; Passadakis and Oreopoulos 2003; Ansari 2011). Sessions vary from 8 to 12 hours, during which 26 to 30-L of dialysate are exchanged. TPD increases solute clearances by increasing the peritoneal contact time for constant clearance while maintaining high dialysate flow rates. One randomized crossover study of 87 patients compared CEPD to TPD in AKI reported higher small solute clearance with TPD (creatinine clearances in ml/min of 9.94 in TPD vs. 6.74 in CEPD, P=0.001; and urea clearance in ml/min of 19.85 in TPD vs. 10.63 in CEPD, P=0.001); ultrafiltration volumes (2.8 L/session TPD vs. 2.0 L/session CEPD, P=0.03), even though the total volume of dialysate per session was the same (26 L) (Chitalia et al. 2002). In the same study, TPD was superior to CEPD in the removal of potassium and phosphate.

29.4.3.5 Continuous Flow PD

Continuous flow PD (CFPD) has regained popularity in recent years and has long been considered to have the highest solute clearance and ultrafiltration of any PD modality (Dell'Aquila et al. 2007; Ronco and Amerling 2006). This technique maintains a certain intraperitoneal volume (2-3L) with a continuous influx and outflow of dialysate without interruptions through the use of double lumen catheters (Ronco and Amerling 2006). This eliminates wasted time during inflow and drain and there is a

continuous concentration gradient for solute clearance. Continuous dialysate flows of 100 to 300 ml/min can be achieved with urea clearances in the range of 30 to 50 ml/min (Amerling et al. 2003). An 8 hour session with CFPD in a 70 kg patient can yield a Kt/V_{urea} 0.58/session or a weekly standardized Kt/V_{urea} 4.0 assuming daily treatments (Cruz et al. 2001). Mean ultrafiltration rates using 1.5% dextrose solution have been reported as 13.4 ml/min in a single pass dialysate system (Cruz et al. 2001). The main limitation for widespread use of this technique is the cost associated with use of commercially available dialysate due to the high dialysate flow rates. The dialysate can be used in a single pass or in a recirculation loop with a regeneration system to lower costs (Dell'Aquila et al. 2007).

29.5 CONCLUSION

PD offers patients a home-based therapy to carry out their dialysis in a variety of different ways, including APD and CAPD. Dose of dialysis has traditionally been measured as small solute clearance (i.e. urea or creatinine) although one may also measure the clearance of middle molecules or protein-bound molecules such as β2-microglobulin or p-cresol. Treatment of acid-base disturbances, electrolyte disorders, and volume disturbances should also be recognized as important functions of PD that are not specifically measured when measuring urea clearance.

Earlier studies suggested the need for a higher level of small solute clearance than was achievable in many patients – these results have been since shown to be a function of RRF. Randomized trials have shown that increasing the dose of PD beyond a peritoneal Kt/V_{urea} of 1.7 (or alternatively increasing the CAPD prescription beyond 2.0-L x 4 exchanges) is not associated with improved quality of life or survival. Nevertheless, some dose of dialysis is important for patients and some data exists that suggests there is a threshold effect of small solute clearance on outcomes in anuric patients.

There are a myriad of patient- and prescription-specific factors that affect the delivered dose of PD (see Fig. 29.5). Although patients with significant RRF can likely initiate on virtually any standard PD therapy, with loss of RRF one may need to tailor the PD prescription to the individual patient. Larger patients may tolerate increased volumes as a means of increasing the dose of PD to patients. More frequent exchanges can be used in either CAPD or APD, one must recognize however that there is a limit to this after which time lost with filling and draining of dialysate becomes an ever-increasing proportion of the total dialysis time. Patients with higher transport status as measured by the PET are better suited to APD with more frequent exchanges and the use of icodextrin as a long dwell,

whereas, patients with lower transport status will tend to do well on CAPD where exchanges are longer, allowing more time for equilibration of solutes. A properly functioning PD catheter is vital to the delivery of PD and hence the achievable PD dose. Understanding the patient's physiological characteristics, personal preferences and social circumstances coupled with a sound comprehension of the principles of PD and the prescription-factors that affect dose will lead to the best care for that patient.

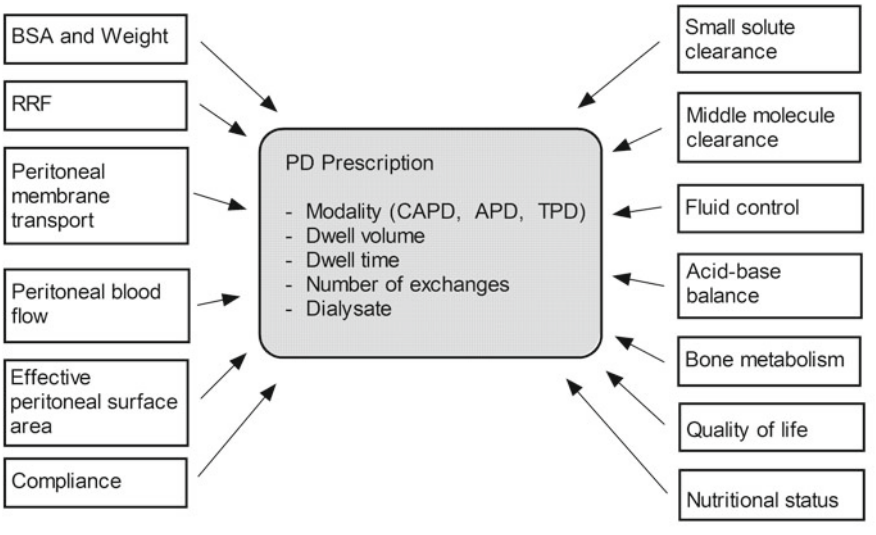


Fig. 29.5 Factors affecting peritoneal dialysis delivered and achieved dose. RRF = residual renal function; BSA = body surface area; SA = surface area

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REFERENCES

Alarabi, A.A., Petersson, T., Danielson, B.G., Wikstrom, B.: Continuous peritoneal dialysis in children with acute renal failure. Adv. Perit. Dial. 10, 289–293 (1994)

Albanese, A.M., Albanese, E.F., Mino, J.H., et al.: Peritoneal surface area: Measurements of 40 structures covered by peritoneum: Correlation between total peritoneal surface area and the surface calculated by formulas. Surg. Radiol. Anat. 31(5), 369–377 (2009)

Amerling, R., Glezerman, I., Savransky, E., et al.: Continuous flow peritoneal dialysis: current perspectives. Contrib. Nephrol. 140, 294–304 (2003)

Amici, G.: Mathematical models for prescription and delivery in peritoneal dialysis. Nephrol. Dial. Transplant. 13(suppl. 6), 120–124 (1998)

Ansari, N.: Peritoneal dialysis in renal replacement therapy for patients with acute kidney injury. Int. J. Nephrol. (2011), doi:10.4061/2011/739794

Ash, S.R., Bever, S.L.: Peritoneal dialysis for acute renal failure: the safe, effective, and low-cost modality. Adv. Ren. Replace Ther. 2(2), 160–163 (1995)

Ates, K., Nergizoglu, G., Keven, K., et al.: Effect of fluid and sodium removal on mortality in peritoneal dialysis patients. Kidney Int. 60(2), 767–776 (2001)

Aune, S.: Transperitoneal exchange. II. Peritoneal blood flow estimated by hydrogen gas clearance. Scand. J. Gastroenterol. 5(2), 99–104 (1970)

Baczyski, D., Antosiewicz, S., Waniewski, J., et al.: Efficacy of peritoneal dialysis during infusion and drainage procedures. Perit. Dial. Int. 30(6), 633–637 (2010)

Bagshaw, S.M., Brophy, P.D., Cruz, D., Ronco, C.: Fluid balance as a biomarker: impact of fluid overload on outcome in critically ill patients with acute kidney injury. Crit. Care 12(4), 169 (2008)

Bargman, J.M., Thorpe, K.E., Churchill, D.N.: CANUSA Peritoneal Dialysis Study Group Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: a reanalysis of the CANUSA study. J. Am. Soc. Nephrol. 12(10), 2158–2162 (2001)

Barone, R.J., Campora, M.I., Gimenez, N.S., et al.: Body surface area, adequacy, and technique failure in chronic peritoneal dialysis. Adv. Perit. Dial. 26, 105–109 (2010)

Bhaskaran, S., Schaubel, D.E., Jassal, S.V., et al.: The effect of small solute clearances on survival of anuric peritoneal dialysis patients. Perit. Dial. Int. 20(2), 181–187 (2000)

Blake, P.G., Bargman, J.M., Brimble, K.S., et al.: Clinical practice guidelines and recommendations on peritoneal dialysis adequacy 2011. Perit. Dial. Int. 31(2), 218–239 (2011)

Blake, P.G., Korbet, S.M., Blake, R., et al.: A multicenter study of noncompliance with continuous ambulatory peritoneal dialysis exchanges in US and Canadian patients. Am. J. Kidney Dis. 35(3), 506–514 (2000)

Blake, P.G., Sombolos, K., Abraham, G., et al.: Lack of correlation between urea kinetic indices and clinical outcomes in CAPD patients. Kidney Int. 39(4), 700–706 (1991)

Bohorques, R., Rivas, R., Martinez, A.: Continuous equilibration peritoneal dialysis (CEPD) in acute renal failure. Perit. Dial. Int. 10(2), 183 (1990)

Bouchet, Y., Voilin, C., Yver, R.: The peritoneum and its anatomy. In: Bengmark, S. (ed.) The Peritoneum and Peritoneal Access, pp. 1–13. Wright, London (1989)

Brandes, J.C., Packard, W.J., Watters, S.K., Fritsche, C.: Optimization of dialysate flow and mass transfer during automated peritoneal dialysis. Am. J. Kidney Dis. 25(4), 603–610 (1995)

Brimble, K.S., Walker, M., Margetts, P.J., et al.: Meta-analysis: peritneal membrane transport, mortality, and technique failure in peritoneal disalysis. J. Am. Soc. Nephrol. 17(9), 2591–2598 (2006)

Bro, S., Bjorner, J.B., Tofte-Jensen, P., et al.: A prospective, randomized multicenter study comparing APD and CAPD treatment. Perit. Dial. Int. 19(6), 526–533 (1999)

Brown, E.A., Davies, S.J., Heimburger, O., et al.: Adequacy targets can be met in anuric patients by automated peritoneal dialysis: baseline data from EAPOS. Perit. Dial. Int. 21(suppl. 3), S133–S137 (2001)

Brown, E.A., Davies, S.J., Rutherford, P., et al.: Survival of functionally anuric patients on automated peritoneal dialysis: the European APD Outcome Study. J. Am. Soc. Nephrol. 14(11), 2948–2957 (2003)

Bundgaard, M.: The three-dimensional organization of tight junctions in a capillary endothelium revealed by serial-section electron microscopy. J. Ultrastruct. Res. 88(1), 1–17 (1984)

Burdmann, E.A., Chakravarthi, R.: Peritoneal dialysis in acute kidney injury: lessons learned and applied. Semin. Dial. 24(2), 149–156 (2011)

Burkart, J.M.: Adequacy of peritoneal dialysis. Adv. Ren. Replace Ther. 7(4), 310–323 (2000)

Burkart, J.M., Schreiber, M., Korbet, S.M., et al.: Solute clearance approach to adequacy of peritoneal dialysis. Perit. Dial. Int. 16(5), 457–470 (1996)

Cameron, J.S., Ogg, C., Trounce, J.R.: Peritoneal dialysis in hypercatabolic acute renal failure. Lancet 1(7501), 1188–1191 (1967)

Cerda, J., Sheinfeld, G., Ronco, C.: Fluid overload in critically ill patients with acute kidney injury. Blood Purif. 29(4), 331–338 (2010)

Chagnac, A., Herskovitz, P., Ori, Y., et al.: Effect of increased dialysate volume on peritoneal surface area among peritoneal dialysis patients. J. Am. Soc. Nephrol. 13(10), 2554–2559 (2002)

Chagnac, A., Herskovitz, P., Weinstein, T., et al.: The peritoneal membrane in peritoneal dialysis patients: estimation of its functional surface area by applying stereologic methods to computerized tomography scans. J. Am. Soc. Nephrol. 10(2), 342–346 (1999)

Chionh, C.Y., Ronco, C., Finkelstein, F.O., et al.: Acute peritoneal dialysis: what is the 'adequate' dose for acute kidney injury? Nephrol. Dial. Transplant. 25(10), 3155–3160 (2010)

Chitalia, V.C., Almeida, A.F., Rai, H., et al.: Is peritoneal dialysis adequate for hypercatabolic acute renal failure in developing countries? Kidney Int. 61(2), 747–757 (2002)

Churchill, D.N., Thorpe, K.E., Nolph, K.D., et al.: Increased peritoneal membrane transport is associated with decreased patient and technique survival for continuous peritoneal dialysis patients. The Canada-USA (CANUSA) Peritoneal Dialysis Study Group. J. Am. Soc. Nephrol. 9(7), 1285–1292 (1998)

Claure-Del Granado, R., Mehta, R.L.: Assessing and delivering dialysis dose in acute kidney injury. Semin. Dial. 24(2), 156–157 (2011)

Cruz, C., Melendez, A., Gotch, F.A., et al.: Single-pass continuous flow peritoneal dialysis using two catheters. Semin. Dial. 14(5), 391–394 (2001)

Daugirdas, J.T.: Peritoneal dialysis in acute renal failure - Why the bad outcome? N. Engl. J. Med. 347(12), 933–935 (2002)

Davies, S.J.: Preserving residual renal function in peritoneal dialysis: volume or biocompatibility? Nephrol. Dial. Transplant. 24(9), 2620–2622 (2009)

Davies, S.J., Mushahar, L., Yu, Z., Lambie, M.: Determinants of peritoneal membrane function over time. Semin. Nephrol. 31(2), 172–182 (2011)

Davis, I.D., Cizman, B., Mundt, K., et al.: Relationship between drain volume/fill volume ratio and clinical outcomes associated with overfill complaints in peritoneal dialysis patients. Perit. Dial. Int. 31(2), 148–153 (2011)

Dell'Aquila, R., Rodighiero, M.P., Spano, E., et al.: Advances in the technology of automated, tidal, and continuous flow peritoneal dialysis. Perit. Dial. Int. 27(suppl. 2), S130–S137 (2007)

Demetriou, D., Habicht, A., Schillinger, M., et al.: Adequacy of automated peritoneal dialysis with and without manual daytime exchange: A randomized controlled trial. Kidney Int. 70(9), 1649–1655 (2006)

Devuyst, O.: Water channels in peritoneal dialysis. J. Nephrol. 23(suppl. 16), S170–S174 (2010)

Devuyst, O., Ni, J.: Aquaporin-1 in the peritoneal membrane: Implications for water transport across capillaries and peritoneal dialysis. Biochim. Biophys. Acta 1758(8), 1078–1084 (2006)

Diaz-Buxo, J.A., Farmer, C.D., Walker, P.J., et al.: Continuous cyclic peritoneal dialysis: a preliminary report. Artif. Organs 5(2), 157–161 (1981)

Diaz-Buxo, J.A., Lowrie, E.G., Lew, N.L., et al.: Associates of mortality among peritoneal dialysis patients with special reference to peritoneal transport rates and solute clearance. Am. J. Kidney Dis. 33(3), 523–534 (1999)

Diaz-Buxo, J.A., Walker, P.J., Chandler, J.T., et al.: Experience with intermittent peritoneal dialysis and continuous cyclic peritoneal dialysis. Am. J. Kidney Dis. 4(3), 242–248 (1984)

Diaz-Buxo, J.A.: Continuous flow peritoneal dialysis: update. Adv. Perit. Dial. 20, 18–22 (2004)

Douma, C.E., de Waart, D.R., Struijk, D.G., Krediet, R.T.: The nitric oxide donor nitroprusside intraperitoneally affects peritoneal permeability in CAPD. Kidney Int. 51(6), 1885–1892 (1997)

Du Bois, D., Du Bois, E.F.: A formula to estimate the approximate surface area if height and weight be known. Arch. Intern. Med. 17, 863–871 (1916)

Erbe, R.W., Greene Jr., J., Weller, J.M.: Peritoneal dialysis during hemorrhagic shock. J. Appl. Physiol. 22(1), 131–135 (1967)

Evanson, J.A., Himmelfarb, J., Wingard, R., et al.: Prescribed versus delivered dialysis in acute renal failure patients. Am. J. Kidney Dis. 32(5), 731–738 (1998)

Evenepoel, P., Bammens, B., Verbeke, K., Vanrenterghem, Y.: Superior dialytic clearance of beta(2)-microglobulin and p-cresol by high-flux hemodialysis as compared to peritoneal dialysis. Kidney Int. 70(4), 794–799 (2006)

Fischbach, M., Haraldsson, B., Helms, P., et al.: The peritoneal membrane: a dynamic dialysis membrane in children. Adv. Perit. Dial. 19, 265–268 (2003)

Fischbach, M., Terzic, J., Dangelser, C., et al.: Improved dialysis dose by optimizing intraperitoneal volume prescription thanks to intraperitoneal pressure measurements in children. Adv. Perit. Dial. 13, 271–273 (1997)

Flanigan, M.J., Doyle, C., Lim, V.S., Ullrich, G.: Tidal peritoneal dialysis: preliminary experience. Perit. Dial. Int. 12(3), 304–308 (1992)

Flessner, M.F.: Peritoneal transport physiology: insights from basic research. J. Am. Soc. Nephrol. 2(2), 122–135 (1991)

Flessner, M., Henegar, J., Bigler, S., Genous, L.: Is the peritoneum a significant transport barrier in peritoneal dialysis? Perit. Dial. Int. 23(6), 542–549 (2003)

Flessner, M.F.: Small-solute transport across specific peritoneal tissue surfaces in the rat. J. Am. Soc. Nephrol. 7(2), 225–233 (1996a)

Flessner, M.F.: The importance of the interstitium in peritoneal transport. Perit. Dial. Int. 16(suppl. 1), S76–S79 (1996b)

Flessner, M.F., Lofthouse, J.: Blood flow does not limit peritoneal transport. Perit. Dial. Int. 19(suppl. 2), S102–S105 (1999)

Fried, L.H.: Higher membrane permeability predicts poorer patient survival. Perit. Dial. Int. 17(4), 387–389 (1997)

Fusshoeller, A.: Histomorphological and functional changes of the peritoneal membrane during long-term peritoneal dialysis. Pediatr. Nephrol. 23(1), 19–25 (2008)

Gabriel, D.P., Caramori, J.T., Martim, L.C., et al.: High volume peritoneal dialysis vs daily hemodialysis: a randomized, controlled trial in patients with acute kidney injury. Kidney Int. 108(Suppl.), 87–93 (2008)

Gabriel, D.P., Nascimento, G.V., Caramori, J.T., et al.: Peritoneal dialysis in acute renal failure. Ren. Fail. 28(6), 451–456 (2006)

Gabriel, D.P., Nascimento, G.V., Caramori, J.T., et al.: High volume peritoneal dialysis for acute renal failure. Perit. Dial. Int. 27(3), 277–282 (2007)

Gastaldi, L., Baratelli, L., Cassani, D., et al.: Low flow continuous peritoneal dialysis in acute renal failure. Nephron. 29(1-2), 101–102 (1981)

George, S., Ryan, L., Fritzsch, S., Miller, R.: A clinical study of 2.5 liter exchange volumes. Adv. Perit. Dial. 5, 72–75 (1989)

Golper, T.A., Twardowski, Z.J., Warady, B.A., et al.: Dose and adequacy. Perit. Dial. Int. 17(suppl. 3), S40–S41 (1997)

Gotch, F.A.: The kinetic spectrum of APD. Semin. Dial. 15(6), 393–396 (2002)

Greene Jr., J.A., Lapco, L., Weller, J.M.: Effect of drug therapy of hemorrhagic hypotension on kinetics of peritoneal dialysis in the dog. Nephron. 7(2), 178–183 (1970)

Harris, K.P., Keogh, A.M., Alderson, L.: Peritoneal dialysis fill volume: can the patient tell the difference? Perit. Dial Int. 21(suppl. 3), S144–S147 (2001)

Harty, J., Boulton, H., Venning, M., Gokal, R.: Impact of increasing dialysis volume on adequacy targets: a prospective study. J. Am. Soc. Nephrol. 8(8), 1304–1310 (1997)

Heimburger, O.: How should we measure peritoneal dialysis adequacy in the clinic. Contrib. Nephrol. 163, 140–146 (2009)

Heimburger, O., Waniewski, J., Werynski, A., Lindholm, B.: A quantitative description of solute and fluid transport during peritoneal dialysis. Kidney Int. 41(5), 1320–1332 (1992)

Himmelfarb, J., Evanson, J., Hakim, R.M., et al.: Urea volume of distribution exceeds total body water in patients with acute renal failure. Kidney Int. 61(1), 317–323 (2002)

Ho-dac-Pannekeet, M.M., Schouten, N., Langendijk, M.J., et al.: Peritoneal transport characteristics with glucose polymer based dialysate. Kidney Int. 50(3), 979–986 (1996)

Hyman, A., Mendelssohn, D.C.: Current Canadian approaches to dialysis for acute renal failure in the ICU. Am. J. Nephrol. 22(1), 29–34 (2002)

Ifudu, O., Feldman, J., Friedman, E.A.: The intensity of hemodialysis and the response to erythropoietin in patients with end-stage renal disease. N. Engl. J. Med. 334(7), 420–425 (1996)

Ifudu, O., Uribarri, J., Rajwani, I., et al.: Adequacy of dialysis and differences in hematocrit among dialysis facilities. Am. J. Kidney Dis. 36(6), 1166–1174 (2000)

Indraprasit, S., Charoenpan, P., Suvachittanont, O., et al.: Continuous peritoneal dialysis in acute renal failure from severe falciparum malaria. Clin. Nephrol. 29(3), 137–143 (1988)

Ivarsen, P., Povlsen, J.V., Jensen, J.D.: Increasing fill volume reduces cardiac performance in peritoneal dialysis. Nephrol. Dial. Transplant. 22(10), 2999–3004 (2007)

Jager, K.J., Merkus, M.P., Dekker, F.W., et al.: Mortality and technique failure in patients starting chronic peritoneal dialysis: results of The Netherlands Cooperative Study on the Adequacy of Dialysis. NECOSAD Study Group. Kidney Int. 55(4), 1476–1485 (1999)

Jansen, M.A., Termorshuizen, F., Korevaar, J.C., et al.: Predictors of survival in anuric peritoneal dialysis patients. Kidney Int. 68(3), 1199–1205 (2005)

Jindal, K., Chan, C.T., Deziel, C., et al.: Hemodialysis clinical practice guidelines for the Canadian Society of Nephrology. J. Am. Soc. Nephrol. 17(suppl. 1), S1–S27 (2006)

Johnson, D.W., Hawley, C.M., McDonald, S.P., et al.: Superior survival of high transporters treated with automated versus continuous ambulatory peritoneal dialysis. Nephrol. Dial. Transplant. 25(6), 1973–1979 (2010)

Juergensen, P.H., Murphy, A.L., Kliger, A.S., Finkelstein, F.O.: Increasing the dialysis volume and frequency in a fixed period of time in CPD patients: the effect on Kpt/V and creatinine clearance. Perit. Dial. Int. 22(6), 693–697 (2002)

Juergensen, P.H., Murphy, A.L., Pherson, K.A., et al.: Tidal peritoneal dialysis: comparison of different tidal regimens and automated peritoneal dialysis. Kidney Int. 57(6), 2603–2607 (2000)

Juergensen, P.H., Gorban-Brennan, N., Finkelstein, F.O.: Compliance with the dialysis regimen in chronic peritoneal dialysis patients: utility of the pro card and impact of patient education. Adv. Perit. Dial. 20, 90–92 (2004)

Kathuria, P., Twardowski, Z.J.: Automated peritoneal dialysis. In: Khanna, R., Krediet, R. (eds.) Nolph and Gokal's Textbook of Peritoneal Dialysis, 3rd edn. Springer US, Boston (2009)

Keshaviah, P.: Urea kinetic and middle molecule approaches to assessing the adequacy of hemodialysis and CAPD. Kidney Int. 40(Suppl.), 28–38 (1993)

Keshaviah, P., Emerson, P.F., Vonesh, E.F., Brandes, J.C.: Relationship between body size, fill volume, and mass transfer area coefficient in peritoneal dialysis. J. Am. Soc. Nephrol. 4(10), 1820–1826 (1994)

Kim, D.J., Do, J.H., Huh, W., Kim, Y.G., Oh, H.Y.: Dissociation between clearances of small and middle molecules in incremental peritoneal dialysis. Perit. Dial. Int. 21(5), 462–466 (2001)

Krediet, R.T., Boeschoten, E.W., Struijk, D.G., Arisz, L.: Differences in the peritoneal transport of water, solutes and proteins between dialysis with two- and with three-litre exchanges. Nephrol. Dial Transplant. 3(2), 198–204 (1988)

Krediet, R.T., Douma, C.E., van Olden, R.W., et al.: Augmenting solute clearance in peritoneal dialysis. Kidney Int. 54(6), 2218–2225 (1998)

Krediet, R.T., Lindholm, B., Rippe, B.: Pathophysiology of peritoneal membrane failure. Perit. Dial. Int. 20(suppl. 4), S22–S42 (2000a)

Krediet, R.T., Zweers, M.M., Van Der Wal, A.C., Struijk, D.G.: Neoangiogenesis in the peritoneal membrane. Perit. Dial. Int. 20(suppl. 2), S19–S25 (2000b)

Krediet, R.T., Zemel, D., Imholz, A.L., et al.: Indices of peritoneal permeability and surface area. Perit. Dial. Int. 13(suppl. 2), S31–S34 (1993)

Krediet, R.T., Zemel, D., Imholz, A.L., Struijk, D.G.: Impact of surface area and permeability on solute clearances. Perit. Dial. Int. 14(suppl. 3), S70–S77 (1994)

Krediet, R.T., Zuyderhoudt, F.M., Boeschoten, E.W., Arisz, L.: Alterations in the peritoneal transport of water and solutes during peritonitis in continuous ambulatory peritoneal dialysis patients. Eur. J. Clin. Invest. 17(1), 43–52 (1987)

Lam, M.F., Tang, C., Wong, A.K., et al.: ASPD: A prospective study of adequacy in Asian patients on long term, small volume, continuous ambulatory peritoneal dialysis. Perit. Dial. Int. 26(4), 466–474 (2006)

Li, P.K., Chow, K.M.: Maximizing the success of peritoneal dialysis in high transporters. Perit. Dial. Int. 27(suppl. 2), S148–S152 (2007)

Li, P.K., Chow, K.M., Wong, T.Y., et al.: Effects of an angiotensin-converting enzyme inhibitor on residual renal function in patients receiving peritoneal dialysis. A randomized, controlled study. Ann. Intern. Med. 139(2), 105–112 (2003)

Lindsay, R.M., Friesen, M., Koens, F., et al.: Platelet function in patients on long term peritoneal dialysis. Clin. Nephrol. 6(2), 335–339 (1976)

Lo, W.K., Ho, Y.W., Li, C.S., et al.: Effect of Kt/V on survival and clinical outcome in CAPD patients in a randomized prospective study. Kidney Int. 64(2), 649–656 (2003)

Lo, W.K., Jiang, Y., Cheng, S.W., Cheng, I.K.: Survival of CAPD patients in a center using three two-liter exchanges as standard regime. Perit. Dial. Int. 16(suppl. 1), S163–S166 (1996)

Lo, W.K., Lui, S.L., Chan, T.M., Li, F.K., et al.: Minimal and optimal peritoneal Kt/V targets: results of an anuric peritoneal dialysis patient's survival analysis. Kidney Int. 67(5), 2032–2038 (2005)

Lysaght, M.J., Pollock, C.A., Moran, J.E., et al.: Beta-2 microglobulin removal during continuous ambulatory peritoneal dialysis (CAPD). Perit. Dial. Int. 9(1), 29–35 (1989)

de Jesus, V.M., Amato, D., Correa-Rotter, R., Paniagua, R.: Relationship between fill volume, intraperitoneal pressure, body size, and subjective discomfort perception in CAPD patients. Mexican Nephrology Collaborative Study Group. Perit. Dial. Int. 20(2), 188–193 (2000)

Maiorca, R., Brunori, G., Zubani, R., et al.: Predictive value of dialysis adequacy and nutritional indices for mortality and morbidity in CAPD and HD patients. A longitudinal study. Nephrol. Dial. Transplant. 10(12), 2295–2305 (1995)

Mehta, R.L., Letteri, J.M.: Current status of renal replacement therapy for acute renal failure. A survey of US nephrologists. The National Kidney Foundation Council on Dialysis. Am. J. Nephrol. 19(3), 377–382 (1999)

Michels, W.M., Verduijn, M., Grootendorst, D.C., et al.: Decline in residual renal function in automated compared with continuous ambulatory peritoneal dialysis. Clin. J. Am. Soc. Nephrol. 6(3), 537–542 (2011)

Movilli, E., Cancarini, G.C., Zani, R., et al.: Adequacy of dialysis reduces the doses of recombinant erythropoietin independently from the use of biocompatible membranes in haemodialysis patients. Nephrol. Dial. Transplant. 16(1), 111–114 (2001)

Mujais, S., Nolph, K., Gokal, R., et al.: Evaluation and management of ultrafiltration problems in peritoneal dialysis. International Society for Peritoneal Dialysis Ad Hoc Committee on Ultrafiltration Management in Peritoneal Dialysis. Perit. Dial. Int. 20(suppl. 4), S5–S21 (2000)

Nagy, J.A.: Peritoneal membrane morphology and function. Kidney Int. Suppl. 56, S2–S11 (1996)

NKF-K/DOQI. NKF-K/DOQI Clinical Practice Guidelines for Peritoneal Dialysis Adequacy: update 2006. American Journal of Kidney Diseases 48(suppl. 1), S1–S322 (2006)

Nolph, K.D.: Peritoneal dialysis for acute renal failure. ASAIO Trans. 34, 54–55 (1988)

Nolph, K.D., Jensen, R.A., Khanna, R., Twardowski, Z.J.: Weight limitations for weekly urea clearances using various exchange volumes in continuous ambulatory peritoneal dialysis. Perit. Dial. Int. 14(3), 261–264 (1994)

Paganini, E.P.: Dialysis is not dialysis is not dialysis! Acute dialysis is different and needs help! Am. J. Kidney Dis. 32(5), 832–833 (1998)

Paniagua, R., Amato, D., Vonesh, E., et al.: Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. J. Am. Soc. Nephrol. 13(5), 1307–1320 (2002)

Paniagua, R., Amato, D., Vonesh, E., et al.: Health-related quality of life predicts outcomes but is not affected by peritoneal clearance: The ADEMEX trial. Kidney Int. 67(3), 1093–1104 (2005)

Paniagua, R., Ventura, M.J., Rodriguez, E., et al.: Impact of fill volume on peritoneal clearances and cytokine appearance in peritoneal dialysis. Perit Dial. Int. 24(2), 156–162 (2004)

Passadakis, P., Oreopoulos, D.: Peritoneal dialysis in acute renal failure. Int. J. Artif. Organs 26(4), 265–277 (2003)

Passadakis, P.S., Oreopoulos, D.G.: Peritoneal dialysis in patients with acute renal failure. Adv. Perit. Dial. 23, 7–16 (2007)

Pawlaczyk, K., Kuzlan, M., Wieczorowska-Tobis, K., et al.: Species-dependent topography of the peritoneum. Adv. Perit. Dial. 12, 3–6 (1996)

Perez, R.A., Blake, P.G., McMurray, S., et al.: What is the optimal frequency of cycling in automated peritoneal dialysis? Perit. Dial. Int. 20(5), 548–556 (2000)

Perl, J., Huckvale, K., Chellar, M., et al.: Peritoneal protein clearance and not peritoneal membrane transport status predicts survival in a contemporary cohort of peritoneal dialysis patients. Clin. J. Am. Soc. Nephrol. 4(7), 1201–1206 (2009)

Phu, N.H., Hien, T.T., Mai, N.T., et al.: Hemofiltration and peritoneal dialysis in infection-associated acute renal failure in Vietnam. N. Engl. J. Med. 347(12), 895–902 (2002)

Pietrzak, I., Hirszel, P., Shostak, A., et al.: Splanchnic volume, not flow rate, determines peritoneal permeability. ASAIO Trans. 35(3), 583–587 (1989)

Piraino, B., Bender, F., Bernardini, J.: A comparison of clearances on tidal peritoneal dialysis and intermittent peritoneal dialysis. Perit. Dial. Int. 14(12), 145–148 (1994)

Prowant, B.F., Moore, H.L., Twardowski, Z.J., Khanna, R.: Understanding discrepancies in peritoneal equilibration test results. Perit. Dial. Int. 30(3), 366–370 (2010)

Qi, H., Xu, C., Yan, H., Ma, J.: Comparison of icodextrin and glucose solutions for long dwell exchange in peritoneal dialysis: a meta-analysis of randomized controlled trials. Perit. Dial. Int. 31(2), 179–188 (2011)

Rabindranath, K.S., Adams, J., Ali, T.Z., et al.: Automated vs continuous ambulatory peritoneal dialysis: a systematic review of randomized controlled trials. Nephrol. Dial. Transplant. 22(10), 2991–2998 (2007)

Rao, P., Passadakis, P., Oreopoulos, D.G.: Peritoneal dialysis in acute renal failure. Perit. Dial. Int. 23(4), 320–322 (2003)

Reznik, V.M., Griswold, W.R., Peterson, B.M., et al.: Peritoneal dialysis for acute renal failure in children. Pediatr. Nephrol. 5(6), 715–717 (1991)

Rippe, B., Stelin, G., Haraldsson, B.: Computer simulations of peritoneal fluid transport in CAPD. Kidney Int. 40(2), 315–325 (1991)

Rippe, B., Venturoli, D., Simonsen, O., de Arteaga, J.: Fluid and electrolyte transport across the peritoneal membrane during CAPD according to the three-pore model. Perit. Dial. Int. 24(1), 10–27 (2004)

Rivetti, M., Battú, S., Barrile, P., et al.: Compliance with automated peritoneal dialysis. EDTNA ERCA J. 28, 40–43 (2002)

Rodriguez, A.M., Diaz, N.V., Cubillo, L.P., et al.: Automated peritoneal dialysis: a Spanish multicentre study. Nephrol. Dial. Transplant. 13(9), 2335–2340 (1998)

Ronco, C., Amerling, R.: Continuous flow peritoneal dialysis: current state-of-the-art and obstacles to further development. Contrib. Nephrol. 150, 310–320 (2006)

Ronco, C., Kellum, J.A., Bellomo, R., House, A.A.: Potential interventions in sepsis-related acute kidney injury. Clin. J. Am. Soc. Nephrol. 3(2), 531–544 (2008)

Rosengren, B.I., Rippe, B.: Blood flow limitation in vivo of small solute transfer during peritoneal dialysis in rats. J. Am. Soc. Nephrol. 14(6), 1599–1604 (2003)

Rubin, J., Clawson, M., Planch, A., Jones, Q.: Measurements of peritoneal surface area in man and rat. Am. J. Med. Sci. 295(5), 453–458 (1988)

Rumpsfeld, M., McDonald, S.P., Johnson, D.W.: Higher peritoneal transport status is associated with higher mortality and technique failure in the Australian and New Zealand peritoneal dialysis patient populations. J. Am. Soc. Nephrol. 17(1), 271–278 (2006)

Rumpsfeld, M., McDonald, S.P., Johnson, D.W.: Peritoneal small solute clearance is nonlinearly related to patient survival in the Australian and New Zealand peritoneal dialysis patient populations. Perit. Dial. Int. 29(6), 637–646 (2009)

Schiffl, H.: Utility of urea kinetic modelling for prescription of adequate intermittent dialysis in critically ill maintenance dialysis patients. Nephrol. Dial. Transplant. 22(7), 2096 (2007)

Schrier, R.W.: Nephrology forum: acute renal failure. Kidney Int. 15(2), 205–216 (1979)

Shinaberger, J.H.: Quantitation of dialysis: historical perspective. Semin. Dial. 14(4), 238–245 (2001)

Sipkins, J.H., Kjellstrand, C.M.: Severe head trauma and acute renal failure. Nephron. 28(1), 36–41 (1981)

Smit, W., Schouten, N., van den Berg, N., et al.: Analysis of the prevalence and causes of ultrafiltration during long-term peritoneal dialysis: a cross-sectional study. Perit. Dial. Int. 24(6), 562–570 (2004)

Steiner, R.W.: Continuous equilibration peritoneal dialysis in acute renal failure. Perit. Dial. Int. 9(1), 5–7 (1989)

Steinhauer, H.B., Keck, I., Lubrich-Birkner, I., Schollmeyer, P.: Increased dialysis efficiency in tidal peritoneal dialysis compared to intermittent peritoneal dialysis. Nephron. 58(4), 500–501 (1991)

Suzuki, H., Kanno, Y., Sugahara, S., et al.: Effects of an angiotensin II receptor blocker, valsartan, on residual renal function in patients on CAPD. Am. J. Kidney Dis. 43(6), 1056–1064 (2004)

Szeto, C.C., Wong, T.Y., Chow, K.M., et al.: The impact of increasing the daytime dialysis exchange frequency on peritoneal dialysis adequacy and nutritional status of Chinese anuric patients. Perit. Dial. Int. 22(2), 197–203 (2002)

Teschan, P.E.: Electroencephalographic and other neurophysiological abnormalities in uremia. Kidney Int. 2(Suppl.), 210–216 (1975)

Teschan, P.E., Ginn, H.E., Bourne, J.R., Ward, J.W.: Assessing the adequacy of dialysis. Proc. Eur. Dial. Transplant. Assoc. 18, 697–705 (1981)

Twardowski, Z.J.: Clinical value of standardized equilibration tests in CAPD patients. Blood Purif. 7(2-3), 95–108 (1989)

Twardowski, Z.J., Moore, H.L., Prowant, B.F., Satalowich, R.: Long-term follow-up of body size indices, residual renal function, and peritoneal transport characteristics in continuous ambulatory peritoneal dialysis. Adv. Perit. Dial. 25, 155–164 (2009)

Twardowski, Z.J., Nolph, K.D., Khanna, R., et al.: Peritoneal equilibration test. Peritoneal Dialysis Bulletin 7(3), 138–147 (1987)

Twardowski, Z.J., Prowant, B.F., Nolph, K.D., et al.: High volume, low frequency continuous ambulatory peritoneal dialysis. Kidney Int. 23(1), 64–70 (1983)

Tzamaloukas, A.H., Garella, S., Chazan, J.A.: Peritoneal dialysis for acute renal failure after major abdominal surgery. Arch. Surg. 106(5), 639–643 (1973)

Tzamaloukas, A.H., Malhotra, D., Murata, G.H.: Gender, degree of obesity, and discrepancy between urea and creatinine clearance in peritoneal dialysis. J. Am. Soc. Nephrol. 9(3), 497–499 (1998)

Tzamaloukas, A.H., Onime, A., Raj, D.S., et al.: Computation of the dose of continuous peritoneal dialysis required for adequate peritoneal urea clearance without taking into account peritoneal transport indices. Adv. Perit. Dial. 23, 122–126 (2007)

Uchino, S., Kellum, J.A., Bellomo, R., et al.: Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 294(7), 813–818 (2005)

van Biesen, W., Heimburger, O., Krediet, R., et al.: Evaluation of peritoneal membrane characteristics: a clinical advice for prescription management by the ERBP working group. Nephrol. Dial. Transplant. 25(7), 2052–2062 (2010)

van den Wall Bake, A.W.L., Kooman, J.P., Lange, J.M., et al.: Adequacy of peritoneal dialysis and the importance of preserving residual renal function. Nephrol. Dial. Transplant. 21(suppl. 2), 34–37 (2006)

Vychytil, A., Lilaj, T., Schneider, B., Horl, W.H., Haag-Weber, M.: Tidal peritoneal dialysis for home-treated patients: should it be preferred? Am. J. Kidney Dis. 33(2), 334–343 (1999)

Walsh, M., Manns, B.J., Klarenbach, S., et al.: The effects of nocturnal compared with conventional hemodialysis on mineral metabolism: A randomized-controlled trial. Hemodial Int. 14(2), 174–181 (2010)

Wang, A.Y., Sea, M.M., Ip, R., et al.: Independent effects of residual renal function and dialysis adequacy on dietary micronutrient intakes in patients receiving continuous ambulatory peritoneal dialysis. Am. J. Clin. Nutr. 76(3), 569–576 (2002)

Wang, A.Y., Wang, M., Woo, J., et al.: Inflammation, residual kidney function, and cardiac hypertrophy are interrelated and combine adversely to enhance mortality and cardiovascular death risk of peritoneal dialysis patients. J. Am. Soc. Nephrol. 15(8), 2186–2194 (2004)

Waniewski, J., Heimburger, O., Werynski, A., Lindholm, B.: Aqueous solute concentrations and evaluation of mass transport coefficients in peritoneal dialysis. Nephrol. Dial. Transplant. 7(1), 50–56 (1992)

Watson, P.E., Watson, I.D., Batt, R.D.: Total body water volumes for adult males and females estimated from simple anthropometric measurements. Am. J. Clin. Nutr. 33(1), 27–39 (1980)

Yerram, P., Karuparthi, P.R., Misra, M.: Fluid overload and acute kidney injury. Hemodial Int. 14(4), 348–354 (2010)

ESSAY QUESTIONS

1. Discuss some of the patient and prescription factors that would violate the assumption that dialysate and plasma urea concentrations are equivalent at the completion of an exchange.
2. Discuss the advantages and disadvantages of increasing fill volume from 2.0-L to 2.5-L in an APD patient on a 9-hour overnight schedule as opposed to increasing the number of exchanges from 5 to 7.
3. Discuss the advantages and disadvantages of using tidal PD as opposed to standard APD.
4. Compare and contrast the factors that influence small solute clearance such as urea from that of a middle molecule such as β2-microglobulin in PD.
5. A patient known to have Low-average transport status on CAPD presents with peritonitis. Three days later the patient now presents with fluid overload. Discuss what has likely happened and suggest a prescription modification to manage the problem.
6. Compare and contrast the four peritoneal membrane transport categories with respect to small solute clearance and ultrafiltration. What is the preferred PD modality for each transport type?
7. A 50 year-old man with diabetes as the cause of his renal failure has been on CAPD for 5 years. He has progressive leg swelling and shortness of breath over the last 2 weeks. Work-up for cardiac disease is non-contributory. His last PET done 1-year ago indicates a High-average transport status. Thinking in terms of patient and prescription-specific factors, what are potential causes?
8. Discuss how residual renal function (RRF) affects the PD dose and ways to preserve it in patients on PD?
9. A patient with known Low membrane transport status has been on NIPD for 5 years and has lost his RRF. His PD prescription consists of 12-L over 8 hours (2-L volumes, 6 exchanges with 1.5% dextrose solution). His last adequacy test showed that he is not meeting targets for small solute removal. He is adamant to stay on APD due to lifestyle factors. What modifications would you make to his PD prescription to improve small solute clearance?
10. What are the advantages and disadvantages of using Continuous Flow PD in the treatment of AKI?

MULTIPLE CHOICE QUESTIONS

Choose the best answer

1. A 70-kg patient with high-average transport status is prescribed 2.0-L x 4 exchanges. His UF is 1.0-L. His estimated peritoneal Kt/V_{urea} is:
   A. 1.70
   B. 1.55
   C. 1.62
   D. 1.83

2. A CCPD patient performs 5 exchanges x 2.0-L over 9 hours and holds 1.8-L during the daytime. His UF overnight is 0.8-L and his UF when he comes on to the cycler machine the next evening is 0.5-L. What is his total drain volume?
   A. 11.8-L
   B. 11.1-L
   C. 12.3-L
   D. 13.1-L

3. A patient on NIPD performs 6 exchanges over 9-hours each night. It takes 8 minutes to fill and 9 minutes to drain each cycle. What is his dwell time for each cycle?
   A. 54 min
   B. 90 min
   C. 73 min
   D. 17 min

4. Which of these factors is a potential drawback to increasing fill volumes in PD patients?
   A. decreased cardiac output
   B. decreased vital capacity
   C. increased patient discomfort
   D. all of the above

5. A patient performs TPD using 2.0-L fill volumes, 50% tidal volumes, and receives 14-L over 8-hours. How many exchanges were performed?
   A. 13
   B. 7
   C. 14
   D. 16

6. You have a CAPD patient on 2.0-L x 3 exchanges a day and you decide to modify the prescription to maximize middle molecule clearance. Which scenario would increase the clearance of middle molecules?

A. increase to 4 exchanges a day
B. convert to NIPD, 7 exchanges over 9-hours
C. convert to TPD using 50% tidal volumes, total volume 14.0-L over 9 hours
D. None of the above

7. Which of the following does not affect drain time in a CAPD patient?

A. malpositioned catheter
B. bore size of catheter
C. drain height
D. none of the above

8. A patient with some RRF whose PET study demonstrated him to have low transport status is initiated on CAPD 4 exchanges with 2.0-L volumes using 1.5% dextrose bags. His initial Kt/Vurea is only 1.5. Which of the following modifications to his prescription would not improve his clearance?

A. conversion of overnight dwell to icodextrin
B. addition of furosemide
C. increase in overnight fill to 2.5-L
D. none of the above

9. TPD is useful in which of the following circumstances?

A. Abdominal pain associated with drainage of the dialysate
B. As a general method to increase small solute clearance
C. Extremely prolonged drain time
D. A and C
E. all of the above

10. Which of the following has been shown to be associated with improved survival in PD patients?

A. increased number of exchanges in CAPD
B. increased number of cycles in APD
C. greater middle molecule clearance
D. residual renal function

11. In a patient with no RRF, the use of APD is most ideal for which membrane transport status?

a) Low
b) Low-average
c) High-average
d) High

12. Which anatomical component of the peritoneal membrane is the major determinant of transport?

A. mesothelium
B. interstitium
C. peritoneal capillary
D. lymphatic

13. According to the three-pore model, which pores transport solute-free water?

A. ultra-small pores
B. small pores
C. large pores
D. ultra-large pores

14. Effective peritoneal surface area is the product of which of the following?

A. permeability x peritoneal size selectivity
B. density of capillaries x anatomic peritoneal surface area
C. vascular peritoneal surface area x peritoneal size selectivity
D. density of capillaries x vascular peritoneal surface are

15. Which PD technique used is AKI can achieve the highest small solute clearance?

A. Continuous Equilibrated PD (CEPD)
B. Continuous Flow PD (CFPD)
C. Intermittent PD (IPD)
D. High-volume PD (HVPD)

16. The weekly residual renal Kt/V_{urea} for an 80 kg man with residual renal urea clearance of 4 ml/min is approximately:

A. 1.04
B. 0.84
C. 0.52
D. 1.22

17. During an episode of acute peritonitis, what transient changes in peritoneal membrane characteristics can be seen?

A. increase in small solute clearance and increase in ultrafiltration
B. decrease in small solute clearance and decrease in ultrafiltration
C. increase in small solute clearance and decrease in ultrafiltration
D. decrease in small solute clearance and increase in ultrafiltration

18. Patient compliance with PD can be assessed with which of the following methods?

A. home visit
B. teledialysis
C. memory cards from cycler machine
D. all of the above

19. What morphological peritoneal membrane changes are typical in long-term PD patients?

A. loss of mesothelium
B. sub-mesothelial fibrosis
C. angiogenesis
D. all of the above

20. In AKI, why may the use of clearance-based dialysis dosage, i.e. Kt/V_{urea} and creatinine clearance be inaccurate?

A. V_{urea} is consistently overestimated
B. urea generation is stable
C. V_{urea} is consistently underestimated
D. none of the above