

Chapter 2

Current Status of Peritoneal Dialysis

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It was in 1923 that Ganter performed the first peritoneal dialysis (PD) in a woman with renal failure [1]. However, the early experience with intermittent peritoneal dialysis (IPD) was discouraging and led to the belief that PD was not an appropriate renal replacement therapy for patients with end-stage renal disease (ESRD) [2]. The introduction of the concept of continuous ambulatory peritoneal dialysis (CAPD) by Popovich et al. in 1976 [3] was initially met with scepticism, but the successful clinical experience in nine patients at two centers in the United States [4, 5] convinced skeptics about the potential of the technique as a viable alternative to hemodialysis. Over the last decades, PD has grown worldwide to become the third most common modality for renal replacement. In this chapter, we will present a brief overview of the major advances in the care of patients undergoing PD.

PD: The Technique

A major innovation early on was the introduction of sterile plastic bags for dialysate [6]. Since then, the basic PD system consists of a PVC bag containing 1.5–3.0 L of dialysate, a transfer set, and a catheter access to the peritoneal cavity. Significant advances in the technique of PD have occurred during the subsequent decades.

Trends in Connectology

The initial bag-and-spike system was recognized to result in an unacceptably high incidence of peritonitis from touch contamination. In Italy, a double-bag Y-set device was developed that used a disconnect system with a flush before fill technique [7]. The early success in Italy was confirmed in several other centers [8–10] and is now the system of choice for PD. Over 90% of all patients in North America, Europe, Australia, and New Zealand now use these disconnect devices [11, 12]. The increased monetary cost of the twin-bag system is more than offset by the reduction in peritonitis rates [13].

Trends in Catheter Design

Tenckhoff's design of the indwelling silicone rubber catheter with two dacron cuffs was instrumental in making IPD a viable long-term therapy for renal replacement [14] and it still remains the most widely used catheter worldwide [15–17]. Several variations in the catheter design have been introduced and include the number of cuffs (single vs. double), design of the subcutaneous pathway (permanently bent or “swan-neck” vs. straight) and the intra-abdominal portion (straight vs. coiled) [18]. Double-cuff catheters were thought to be associated with a lower incidence of both peritonitis [16, 19, 20] and exit-site infections [21, 22]. However, in a prospective randomized comparison no significant differences between catheters with single or double cuffs could be established with respect to catheter survival, episodes of peritonitis, and exit site infections [23]. The benefit of the swan-neck design was demonstrable in the United States Renal Data System (USRDS) study only after adjusting for possible center effects [16]. Similarly, no convincing evidence exists for the superiority of the coiled design of the intraperitoneal portion of the catheter [18]. Finally, a downward-directed exit site was thought to result in a reduction in the incidence of exit-site infections and peritonitis

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[19, 24], but in a prospective comparison, catheter types employing downward and lateral tunnel-tract and exit-site configurations produced equivalent outcomes for infectious and mechanical complications [25].

Innovations in connectology and catheter design have resulted in a 1-year catheter survival of over 80% [24]. The skills of the surgeon or nephrologist involved in the implantation of the catheter and the dedication of the PD team involved in postoperative catheter care now seem to be the most important predictors of catheter survival and complications.

Trends in Peritoneal Dialysis Solutions (PDS)

Initially, glucose-based dialysate was the only PDS available. The osmotic agent glucose was buffered with lactate (or, in the early years, with acetate) to produce a low pH of 5.2 to avoid the caramelization during heat-sterilization of the PDS. The limitations of the currently available bioincompatible glucose-based solutions are now widely recognized [26]. The areas of concern are the role of glucose in the nonenzymatic glycation, formation of advanced glycosylation end-products (AGE) and glucose degradation products (GDP), and the unphysiological pH and buffer combinations. Glucose and GDPs are the most likely causative agents being responsible for ultrafiltration failure in PD patients [27–29] (Fig. 2.1). To overcome these and other concerns, alternative solutions have been designed, each targeted to achieve a clinical goal (Table 2.1).

In order to minimize acidity of the peritoneal fluid and reduce GDP production, multibag systems are currently commercially available. In these systems, the buffer is separated from the glucose solution, allowing the glucose to be stored at a very low pH and thus minimizing the formation of GDPs during heat-sterilization. Low GDP solutions have been marketed and demonstrate improved biocompatibility. Preliminary evidence shows a salutary effect on preservation of residual renal function and retrospective analyses suggest a survival advantage with these solutions [30, 31]. These findings, however, need to be confirmed in prospective, randomized clinical trials.

Icodextrin (Extraneal[®]) is a glucose polymer that has undergone clinical trials since the early 1990 s. The molecular size of the icodextrin molecule is substantially larger than that of glucose and is removed from the peritoneal cavity slowly via the lymphatics. This allows for sustained ultrafiltration during the long dwells. The use of 7.5% icodextrin for an overnight exchange in patients with CAPD can generate 3.5 times greater ultrafiltration at 8 h than the 1.5% dextrose solution and similar to the 4.25% dextrose solution [32]. The amount of ultrafiltration with icodextrin can be further augmented by adding nitroprusside and this is associated with an increase in urea and creatinine clearances [33]. When used instead of standard glucose solutions for the long daytime dwell in patients on continuous cyclic peritoneal dialysis (CCPD), it generates significantly greater ultrafiltration, increased peritoneal clearance, and increased sodium removal [34, 35]. In high-average and high transporters, the ultrafiltration during the long daytime CCPD dwell with icodextrin is superior to that obtained with 4.25% dextrose [36]. In short-term clinical studies, no

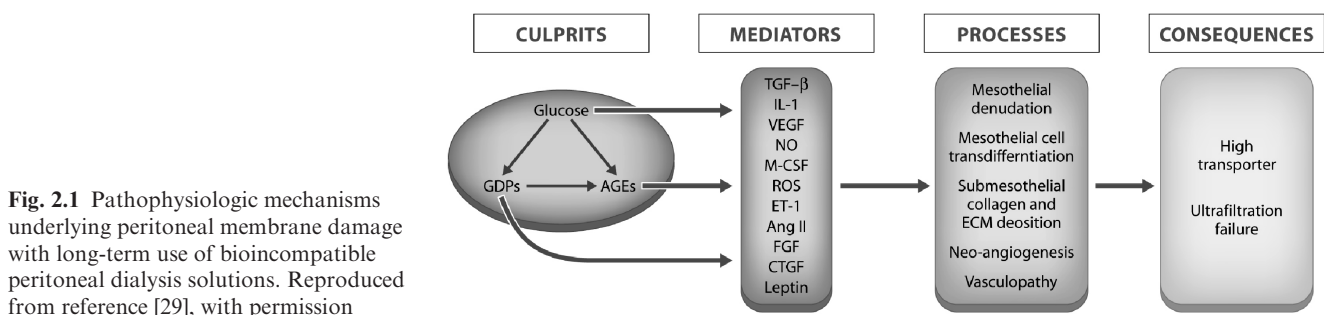


Fig. 2.1 Pathophysiologic mechanisms underlying peritoneal membrane damage with long-term use of bioincompatible peritoneal dialysis solutions. Reproduced from reference [29], with permission

Table 2.1 Biocompatibility of the new peritoneal dialysis solutions

	Low GDP solutions	Bicarbonate/lactate	Amino acid	Icodextrin
Improved pH	✓	✓	✓	
Bicarbonate buffer		✓		
Iso-osmolar				✓
Reduced GDPs	✓	✓	✓	
Reduced AGE formation	✓	✓	✓	✓
Glucose-sparing			✓	✓

significant adverse effects were noticed although serum maltose levels increased in both CAPD and CCPD patients [32, 37]. In later observations, the development of a skin rash appeared to be the most common treatment-related side effect of the use of icodextrin [38, 39]. There was no increase in the episodes of bacterial peritonitis, and during such episodes no further increase in maltose concentration occurred [40]. In response to an excess of cases of aseptic peritonitis in PD patients using icodextrin, a global recall of some batches of icodextrin PDS was issued in May 2002. Extensive analysis revealed that these cases were due to contamination of dialysate with *Alicyclobacillus* [41]. This problem has been resolved. With the recognition of the importance of ultrafiltration in determining patient outcome, icodextrin PDS are increasingly being used in clinical practice in many countries.

Nutrineal[®] is a 1.1% amino acid-containing solution with an ultrafiltration capacity equivalent to 1.5% dextrose PDS. Nutrineal[®] contains no glucose and GDPs and, like icodextrin, has been shown to be more biocompatible to the peritoneal membrane than the conventional PDS [42, 43]. Even though Nutrineal[®] induces anabolism in malnourished PD patients [44], the clinical benefit of improvement in nutritional status in randomized, controlled trials has been modest [45–47]. Providing a surfeit of calories, as obtained with co-administering amino acid and glucose PDS during night-timing cycling, may enhance the nutritional benefits of these solutions [48].

To gain the maximum benefits of biocompatibility and avoidance of glucose and GDP exposure, it is likely that future developments will focus on a combination of products. More prospective outcome-based studies, particularly focusing on the systemic effects of the new solutions, compared to those obtained by comparing these solutions with conventional PDS, will be required to convince health-care providers to pay the higher costs of the new solutions.

Automated Peritoneal Dialysis

Automated peritoneal dialysis (APD) refers to all forms of peritoneal dialysis employing a cyclor to perform the dialysis exchanges. APD regimens include CCPD, IPD, nocturnal intermittent peritoneal dialysis (NIPD), and tidal peritoneal dialysis (TPD). In early experiences with CCPD this modality was shown to be accompanied by lower rates of peritonitis and hospital admissions, whereas it was as effective as CAPD with a Y-connector for patient and technique survival [49]. However, some of the later studies have not been able to confirm the lower incidence of peritonitis in APD patients [50]. The most important advantage of APD compared to CAPD seems the better quality of life and its surrogate, ‘patient preference’ [50, 51].

Assisted Peritoneal Dialysis

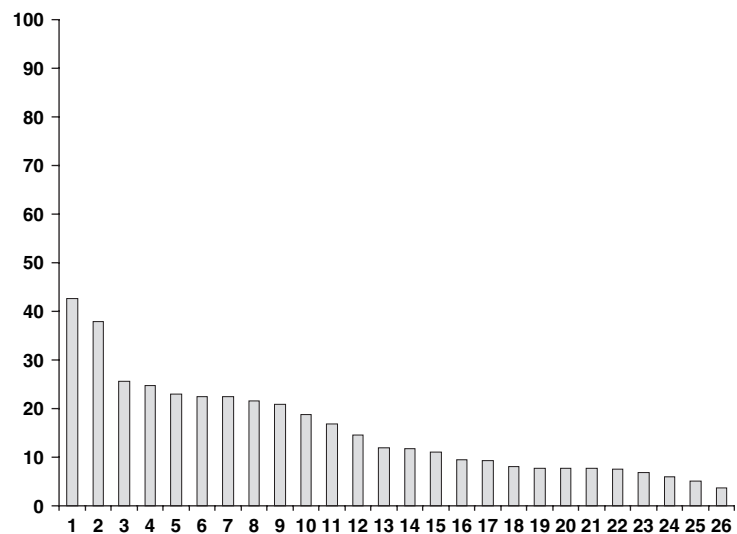
CAPD and APD are home-based dialysis modalities such that patients are trained to perform the treatment themselves. However, in many societies, the elderly, who generally have a higher co-morbidity burden, constitute a progressively larger cohort of incident dialysis patients. These patients are less likely to start or to continue on peritoneal dialysis because they are not able to perform the PD exchanges or to operate the PD cyclers themselves. Many centers have demonstrated the feasibility and safety of assistance for PD treatment by district or private nurses, at the patient’s home, for physically dependent or elderly patients [52–54]. However, in a study from France, patients undergoing assisted PD appeared to have a higher risk of peritonitis than family-assisted patients, unless additional regular home visits were organized by the original training center [55]. Therefore, regular home visits by the training center may be necessary to optimize the care provided by the home nurse.

Epidemiology

Patient Numbers on PD

During the 1980s there occurred a rapid growth in the utilization of PD. This rapid growth continued between 1990 and 1995, with annual global growth rates reaching 15% for the period 1991–1994 [11]. At the end of 1997 the chronic PD population worldwide was estimated to be 115,000, representing 14% of global dialysis patients [56]. However, since then the growth in use of PD has been slower than the increase in the number of patients undergoing maintenance dialysis worldwide [57, 58]. At the end of 2004, 149,000 patients were undergoing PD, representing 11% of the total dialysis population (i.e., 1,371,000). The reasons for this slow-down in the proportion of PD patients seem multifactorial. As the utilization of PD is declining, particularly among the elderly [54, 59], and the elderly are the largest and

Fig. 2.2 Percentage of prevalent dialysis patients on PD in selected countries worldwide. Data obtained from reference [57]. Index for countries: 1, New Zealand; 2, Iceland; 3, Netherlands; 4, Denmark; 5, Korea; 6, Australia; 7, Sweden; 8, Scotland; 9, Finland; 10, Canada; 11, Norway; 12, Philippines; 13, Italy; 14, Turkey; 15, Israel; 16, Malaysia; 17, Greece; 18, Russia; 19, Taiwan; 20, United States; 21, Uruguay; 22, Czech Republic; 23, Thailand; 24, Chile; 25, Germany; 26, Japan



fastest growing group of patients with chronic disease, barriers to self-care PD may contribute. Also, the burden of unrealistic high solute clearance targets might have reinforced the notion of PD as an ‘inadequate’ therapy for renal replacement [60]. Finally, institutional changes in the delivery of dialysis therapy – e.g., proliferation of hemodialysis units and corporatization of dialysis care in the United States – are important contributors to this declining trend.

The wide variations in the utilization of PD in different countries are striking [61]. The proportion of patients on dialysis treated with PD varies from 2 to 4% in countries such as Chile, about 5 to 10% in France, Germany, and the United States, 20 to 30% in the Scandinavian countries, The Netherlands, Australia, and Canada, and >75% in Mexico and Hong Kong (Fig. 2.2) [58, 61]. Even within the same country there are wide variations in the use of PD. In the United States, the prevalence of PD in 2004 ranged from 5% in New York to 10.8% in Network 16 (Alaska, Idaho, Montana, Oregon, and Washington) [57]. In Italy, the disparity in use of PD among regions has increased, varying from 0 to 55% [62]. Finally, in France, there are large differences in the use of PD and the percentage of patients treated with PD can vary from 0 to 22% between different towns in the same region [63]. On the other hand, more recently, in Romania, the share of the dialysis pool of incident patients has increased from 10% in 1995 to 29% in 2004 [64]. The reasons for these differences are multiple and complex and are discussed in a subsequent section.

Growth of Automated PD (APD)

While in the 1980s and the early 1990s the growth in PD was almost entirely due to the expansion of CAPD programs, it is the growth in automated PD that is sustaining the ongoing increase in the number of patients on PD [58, 65, 66]. This growth has been mainly driven by patient preference and the development of new, simpler cyclers [67]. It is anticipated that the use of APD will continue to expand.

Factors Affecting the Choice of PD

The disparity in the use of PD in different countries and different parts of the same country has stimulated tremendous interest in elucidating the factors that determine the choice of PD as the modality for renal replacement. A large number of factors impact upon this choice (Table 2.2).

Medical and Psychosocial Factors and Patient Education

For technical reasons, PD is the modality of choice in infants and small children with ESRD [68]. The presence of medical contraindications to PD is more frequent than that for maintenance HD [69]. In a recent analysis from the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) study, previous major abdominal surgery was the most common medical contraindication followed by cystic kidneys, poor lung function, chronic inflammatory

Table 2.2 Factors determining the utilization of peritoneal dialysis in different parts of the world

<i>Economic factors</i>
Cost of peritoneal dialysis fluids and manpower
Health care system
Physician/facility reimbursement
Resource availability
<i>Psychosocial factors</i>
Physician bias
Educational deficits (physician/patient)
Time of referral
Patient preference/lifestyle attributes
<i>Medical factors</i>
Age
Cardiovascular instability
Availability of vascular access
Abdominal pathology

bowel disease, and poor cardiac condition. Poor cardiac condition was the most frequent medical contraindication to HD. Most patients deemed to have a social contraindication to PD were judged by the nephrologist to be incapable of performing the treatment by themselves. The percentage of patients having any contraindication to PD increases with age. However, studies show that up to 70% of adults have neither medical nor social contraindications to either maintenance HD or chronic PD [70–72].

Predialysis care is associated with a greater probability of selection of PD [69, 73–75]. However, if one accounts for the adequacy of education about dialysis modalities, delayed referral may not be as strong an impediment to the selection of home dialysis modalities [71, 76]. Consistent with these observations, adequate predialysis education is associated with a far higher probability of choosing home dialysis [77]. Furthermore, structured, two-step patient education has been shown in a randomized, controlled trial to be associated with significant increase in the proportion of patients that plan to start home dialysis therapy [78].

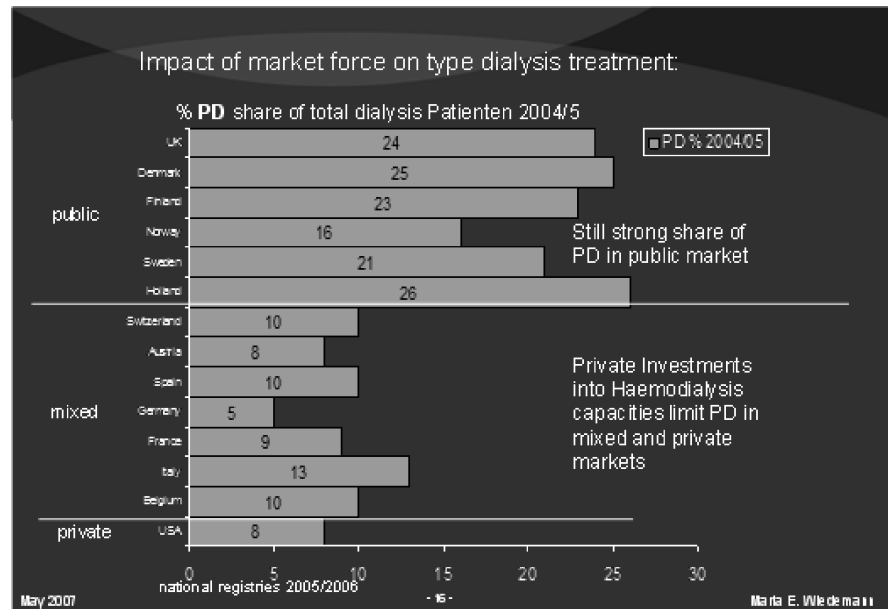
Physician Bias and Patient Education

Physician bias probably also plays an important role in the utilization of PD [62, 63, 79]. The nature of patient education is dependent on the physician bias, and in nonurgent situations the decisions of patients depend mostly on the information provided by their doctors. In the Dialysis Morbidity and Mortality Study (DMMS), Wave 2, only 25% of the patients who chose HD reported that PD was discussed with them, whereas 68% of the patients who chose PD reported that HD was discussed with them [80]. In fact, 84% of the PD patients but only 47% of the HD patients enrolled in the DMMS Wave 2 study appeared to contribute substantially to the decision about their own dialysis modality. A more recent study from the United States confirms the finding that the majority of patients are not presented with the choice of either chronic PD, home HD, or renal transplantation (66, 88, and 74%, respectively) [71]. An incomplete presentation of treatment options is an important reason for underutilization of home dialysis therapies and probably delays access to transplantation. In societies where such an impediment exists, reimbursement for pre-ESRD education may ensure timely access to different renal replacement therapies.

Economic Factors

The effect of economic factors on the selection of dialysis modality may vary by the region of the world. In Europe and America, it appears that the greater the involvement of the “public” (as opposed to “private”) facilities in the provision of dialysis care, the larger the proportion of dialysis patients on chronic PD (Fig. 2.3) [62, 63, 79, 81, 82]. In these areas of the world, the cost of health-care workers in the provision of dialysis therapy is greater than the cost of dialysis supplies. Thus, the delivery of personnel-intensive therapy like hemodialysis is more expensive than a therapy that uses a larger amount of supplies, viz., PD [82]. However, in many Asian and African countries, manpower is substantially cheaper than the cost of dialysis supplies, which are often imported from Western countries. This makes hemodialysis more economical than PD in these societies [83]. Manufacture of dialysis solutions in the developing countries has gone a long way in making PD affordable in some of these societies.

Fig 2.3 Use of PD as a modality for dialysis in various countries during the mid-1990s, based upon the funding of the dialysis provider. The top panel (Japan, USA) shows predominantly private dialysis providers; the middle panel (Germany, Belgium, Austria, Spain, France, Italy) shows a mixture of public and private providers, and the bottom panel (Switzerland, Sweden, Norway, Netherlands, Denmark, Finland, Canada, UK) shows predominantly public providers [81]



Physician reimbursement is significantly influenced by the health-care system and has been identified as a most important determinant of the choice of PD by some [62, 63, 79]. However, financial incentives in Canada (province of Ontario), Germany, and the United States have not translated into a greater utilization of PD [84, 85].

Outcome of PD

HD and PD: Comparative Survival

The current practice of care of the ESRD patient is based on the premise that HD and PD are equivalent therapies. Over the past 20 years, many studies have compared mortality risks in HD and PD [86–94]. Even though at first the results of these studies appear conflicting, some common themes have emerged. First, that the relative risk for death for PD versus HD varies by time over therapy such that most subgroups of patients have a survival advantage during the first 1–2 years of therapy [95]. Second, the lower the co-morbidity burden, the greater is the initial survival advantage associated with PD. In contrast, a higher co-morbidity burden diminishes the advantage of PD and may even be associated with an increased risk after 1–2 years [95]. Notwithstanding these conclusions, it remains unclear if any of the differences in the outcomes can be attributed to the dialysis modality and may simply represent residual confounding from the inability of our statistical tools to adjust for differences in the patient characteristics. Given these caveats, patient choice should probably take precedence in the selection of dialysis modality.

Technique Survival

Technique failure is often used to describe the outcome of PD patients and usually implies cessation of use of PD due to transfer to HD, after censoring for death or transplantation. Based on the published studies, technique survival varies considerably in different countries as well as between different centers in the same country [15, 96–101]. The difference in technique success between PD and HD is greatest in the youngest patients and progressively diminishes in the other age groups [102]. Furthermore, some racial groups may have a lower short-term technique survival than others [97] and patients who are referred late are more likely to be transferred to HD than those who are referred early [103]. With improvements in patient selection, training, and aggressive management of complications, it is possible to obtain 1-year technique survival in excess of 80% [104, 105].

If death and transplantation are excluded, infectious complications have been the most common reason for transfer-out from PD [24, 106, 107]. However, with refinements in technology there has been a significant reduction in the rates of infectious complications. This has been paralleled by an increasing recognition of the importance of

small solute clearance and ultrafiltration capacity. Consistent with the importance of ultrafiltration, retrospective studies have demonstrated that it may be possible to prolong the time for which patients are treated with PD with the use of icodextrin PDS [108, 109].

Adequacy of Small Solute Clearances

In the early years of PD it was commonly accepted that subjective clinical judgment was enough for determining that a patient was well dialyzed [110]. Even though the concept of urea kinetic modeling was first extended to PD in the mid-1980s [111], it was not until the 1990s that this issue was systematically investigated [112–115]. The multicenter CANUSA study [115] showed that both total weekly Kt/V_{urea} and creatinine clearance (peritoneal + renal) were strong predictors of patient survival, and survival improved continuously with increasing total small solute clearance, without an apparent threshold. Higher dialysis dose, including residual renal function, was also associated with better technique survival and less hospitalization. The similar results from the study of Maiorca et al. [114] supported the CANUSA findings and both provided the evidence for the DOQI guidelines published in 1997 [116]. The DOQI guidelines recommended a target Kt/V_{urea} of 2.0 per week and creatinine clearance of 60 L/week/1.73 m² body surface area for CAPD. Somewhat higher levels were recommended for APD. Reanalysis of the CANUSA study, however, revealed that the effect of solute removal on outcome was entirely attributable to the effect of residual renal function [117]. In order to bypass the influence of residual renal function, the effect of the dialysis dose on outcome has been evaluated in four studies of anuric subjects; these studies suggest a minimum threshold of peritoneal Kt/V_{urea} of 1.5–1.7 [118–121]. However, as none of these studies was randomized, confounding cannot be excluded. Consistent with these observational studies, two randomized controlled clinical trials were unable to demonstrate an improvement in survival by increasing the peritoneal small solute clearances within the range currently achieved in clinical practice [122, 123].

Based on these observations, various expert groups now recommend a minimum, total Kt/V_{urea} of 1.7 [60, 124]. Furthermore, it has been recognized that besides solute removal, achievement of euvolemia should be an important goal of adequate dialysis [120, 124].

Residual Renal Function

Not surprisingly, residual renal function (RRF) influences morbidity, mortality, and quality of life in chronic dialysis patients [117, 125–129]. RRF not only contributes to small solute removal, but, probably even more importantly, allows for better volume control and larger-molecular weight solute clearances and continued endocrine and metabolic function [60]. As RRF has a major impact on the outcomes of chronic dialysis patients, its preservation is of major importance.

Decline Rate of Residual Renal Function in PD

Several studies have shown that RRF is better preserved in PD than in HD patients [130–133]. In the NECOSAD study, a large prospective cohort of HD and PD patients in the Netherlands [133], the decline of RRF in HD and PD patients was most pronounced during the first 3 months after the start of treatment. At all time points (0, 3, 6, and 12 months) unadjusted RRF values were higher in PD patients when compared to HD patients. Also after adjustment for baseline variables, PD patients had a 30% higher RRF than HD patients ($p < 0.0001$). Moreover, after adjustment for baseline RRF, the relative difference increased over time, especially during the first 6 months. However, the absolute decrease in both groups was about equal. Proteinuria, a higher diastolic blood pressure, hypotensive episodes in HD, and episodes with dehydration in PD appeared to be associated with a more rapid decline of RRF. In contrast to other studies [134, 135], but in line with the study of de Fijter et al. [136], no detrimental effect of APD on RRF could be found.

Preservation of Residual Renal Function

Considering the importance of RRF to the outcome of dialysis treatment, we need to develop treatment plans that focus on preserving RRF in PD patients [137]. This begins with regular monitoring of RRF and this should be done with a 24-h collection of urine every 1–3 months to measure volume and urea and creatinine clearances. In view of

substantial tubular secretion of creatinine at low GFRs, arithmetic mean of urea and creatinine clearance may be a better measure [138, 139]. Blood pressure should be well controlled and hypotensive episodes should be avoided. Randomized, controlled clinical trials have demonstrated that the benefit of angiotensin converting enzyme inhibitors and angiotensin receptor blockers is seen even at the low levels of glomerular filtration rates reported in patients undergoing PD [140, 141]. The use of diuretics for the preservation of RRF is controversial [142]. Loop diuretics produce an increase in diuresis and may result in a clinically meaningful improvement in fluid balance. However, loop diuretics have no effect on preserving solute clearances [143]. Finally, nephrotoxic agents like aminoglycosides, nonsteroidal anti-inflammatory drugs, and iodinated contrast agents should be avoided as far as possible.

Incremental Peritoneal Dialysis: Are Renal and Peritoneal Clearances Equivalent?

Even though targets have been set for small solute clearance clearances for patients undergoing maintenance dialysis, patients with chronic renal failure are allowed to dwindle to clearances far below the adequacy target before dialysis is initiated [115, 144, 145]. Based on the similar relationship between dietary protein intakes and clearances in pre-dialysis patients and PD patients, the 1997 Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommended that the level of small solute clearances considered to provide adequate CAPD at that time (weekly Kt/V_{urea} , 2.0) be considered the level of renal function at which chronic dialysis should be initiated [116, 146]. The PD subcommittee of the KDOQI recommended that chronic dialysis may be initiated in an incremental fashion such that the sum of the renal and dialytic weekly Kt/V_{urea} should remain near 2.0 at all times. Even though scientific evidence for this approach was lacking, “incremental dialysis” seemed rational. In subsequent studies, this approach could not be validated [147, 148]. A reason for this lack of evidence may have been the assumption that renal and peritoneal solute clearance are equivalent. Even when the measured small solute clearances are identical, clearances for middle and larger molecular weight solutes may differ considerably. Furthermore, the kidney has many other metabolic and endocrinologic functions. Therefore, 1 mL/min of solute clearance by the kidney is of more value to the patient than 1 mL/min solute clearance by the kidney [137].

Nutritional Status

Protein energy wasting at the time of initiation of dialysis, and subsequently, is an important surrogate marker of an adverse patient outcome. This observation makes the assessment of nutritional status and prevention of protein energy wasting an important clinical priority.

Prevalence of Protein Energy Wasting

Protein energy wasting is widely prevalent in the PD population [115, 149, 150]. It is estimated that 40% of PD patients have protein energy wasting, with 5–10% of patients demonstrating severe malnutrition [151]. Since peritoneal glucose absorption contributes to the total energy intake of a PD patient, suboptimal protein intakes are probably more important than suboptimal energy intakes as a cause of nutritional decline [151].

The Malnutrition Inflammation Atherosclerosis (MIA) Syndrome

Several studies have shown that malnutrition, inflammation, and atherosclerotic vascular disease are inter-related and each is associated with mortality [152–155]. The combination of these three conditions has been referred to as the MIA syndrome [156]. Several theories have been proposed to explain the supposed links between the three components of the MIA syndrome [155, 157, 158], but the mechanisms involved are not yet clear. Stenvinkel et al. [156] suggested two types of protein energy wasting in ESRD patients: the first type (type 1) is associated with the uremic syndrome per se or factors associated with uremia such as physical inactivity, underdialysis, dietary restrictions, and psychosocial factors. This type is characterized by a modest reduction in serum albumin due to a low dietary intakes. Significant co-morbidity and signs of inflammation are usually not present in type 1 protein energy wasting and this condition may be addressed by eliminating the causative factors. On the other hand, type 2 protein energy wasting, characterized by significant co-morbid conditions, severe hypoalbuminemia, and an inflammatory response evidenced by higher levels of CRP and pro-inflammatory cytokines, may be more difficult to treat.

Losses of Nutrients in the Dialysate

From the beginning of the CAPD era, it has been recognized that PD is associated with protein losses in the dialysate [159–162]. In the guidelines for nutrition in chronic renal failure, these losses have been taken into account [163, 164]. A recent study suggests that APD may be associated with somewhat higher protein losses compared to previous reports in CAPD patients, and the magnitude of these losses may be related to the number of nighttime exchanges and the duration of dwell [165]. Protein and amino acid losses accounted for an average of 15% of total nitrogen appearance, accounting for almost a third of the increase in dietary protein requirements in CPD patients.

Strategies to Improve Protein Energy Wasting in PD Patients

Several interventions have been shown to improve protein energy wasting in dialysis patients [151]. It is unclear, however, if improvement in nutritional status will result in a reduction in morbidity or mortality of our patients. A detailed discussion is beyond the scope of this chapter but are summarized in Table 2.3 and some of the key issues are summarized below.

Residual Renal Function

RRF plays an important role in maintaining the nutritional status of patients on chronic dialysis [115, 149, 166]. In an international study, loss of RRF correlated with muscle wasting and contributed to anorexia and the symptoms of severe malnutrition [149]. Likewise, in the Canadian–USA (CANUSA) multicenter study, after 6 months of initiation of PD there was a progressive decline in nutritional parameters with declining residual renal function [115]. Hence, preserving residual renal function should be an important goal.

Small Solute Clearances

Several cross-sectional studies have shown a relationship between the peritoneal clearances, dietary protein intake, and the nutritional status of patients [167, 168]. In the CANUSA study, during the first 6 months of CAPD, the addition of dialytic clearances resulted in a marked increase in solute clearances. This was associated with significant improvements in several estimates of nutritional status (subjective global assessment, protein catabolic rate, and lean body mass) and these changes were significantly correlated with the estimates of the dose of dialysis [169].

Table 2.3 Recommended interventions to improve nutritional status in PD patients

Treat reversible causes of anorexia
Improve/maintain small solute clearances
Prokinetic agents for gastroparesis
Treat <i>Helicobacter pylori</i> infection
Increase supply of nutrients
Nutritional counseling
Appetite stimulants
Oral supplements
Enteral supplements
Intraperitoneal amino acids
Correct metabolic acidosis
Anabolic hormones
Recombinant human growth hormone
Insulin-like growth factor I
Nandrolone acetate
L-carnitine
Potential anti-inflammatory therapies
Treatment of co-morbid conditions

Source: Adapted, with permission, from reference [151]

Correction of Metabolic Acidosis

The adverse impact of chronic metabolic acidosis on nutritional status has long been recognized [170]. Two randomized, controlled clinical trials among patients undergoing PD have demonstrated that correction of metabolic acidosis is associated with improvement of nutritional status and reduced hospitalization rates [171, 172].

Use of Intraperitoneal Amino Acid (IPAA) Solutions

Earlier studies with amino-acid solutions enrolled small numbers of patients, were uncontrolled, and used solutions not available commercially. However, three trials supported the use of these solutions. Two metabolic balance studies have demonstrated that IPAA solutions induce anabolism, particularly when a surfeit of calories (as with glucose-based dialysate) is provided [44, 48]. However, subsequent randomized, controlled clinical trials have demonstrated that the nutritional benefits of IPAA solutions may be modest (reviewed in [151]).

Obesity

Early papers on CAPD focused on weight gain during peritoneal dialysis as an undesirable complication [173–176]. Many PD patients experience significant weight gain upon initiation of therapy, but weight usually stabilized thereafter [174, 176]. The weight gain appears to correlate with the daily amount of glucose absorbed from the dialysate [173] and seems to be most prominent in patients who are already obese at the start of treatment [174]. More recently, the impact of obesity on outcomes of dialysis patients has been questioned. Unlike the observations in the general population, in HD patients obesity appears to be associated with improved survival [177]. The advantage associated with obesity in PD patients appears, though, to be less pronounced [178, 179]. In a report from the Australian and New Zealand registry, among patients undergoing PD, obesity was associated with worse outcomes [180] and a higher risk for peritonitis [181]. The effects of weight gain on outcomes of PD patients, thus, need further study.

Cardiovascular Disease

Vascular complications are the major cause of death in patients undergoing PD and include congestive heart failure, myocardial infarction, and cerebrovascular disease. While traditional risk factors like diabetes mellitus, hypertension, smoking, physical inactivity, obesity, and hyperlipidemia contribute substantially to cardiovascular disease in the general population, nontraditional risk factors like inflammation, anemia, and abnormal mineral metabolism are probably also important in dialysis patients [182]. These factors represent only some of the many nontraditional factors that may play a pathophysiologic role in the high cardiovascular burden in dialysis patients.

As discussed above, inflammation, indicated by elevated serum concentrations of acute phase proteins or cytokines, is associated with worse outcome in dialysis patients. Inflammation interacts with many pathophysiologic pathways that lead to vascular damage [183]. Emerging evidence indicates that loss of RRF may be associated with worsened inflammation and left ventricular hypertrophy and they may interact to increase mortality and cardiovascular death risk of PD patients [184].

There is substantial evidence that treatment of anemia in dialysis patients improves quality of life and objective markers of physical and cognitive performance [185, 186]. Furthermore, anemia has been shown to contribute to left ventricular hypertrophy [187]. Even though many epidemiological studies have consistently demonstrated an inverse relationship between hemoglobin levels and mortality, complete correction does not seem to lead to any improvement in survival over partial correction of anemia [188]. A randomized clinical trial of normalization of hemoglobin with erythropoietin in HD patients with cardiovascular disease was stopped prematurely as interim analyses suggested that continuation of the study was unlikely to prove the primary hypothesis [189]. There was a trend towards a higher mortality in the intervention group but this did not reach statistical significance. Thus, based on the current body of evidence, complete correction of anemia cannot be recommended for dialysis patients at this time.

Abnormal mineral metabolism is common in patients with chronic kidney disease and epidemiologic studies suggest that these abnormalities are associated with a higher cardiovascular risk [190]. It seems that hyperphosphatemia is a much stronger predictor of outcome in dialysis patients than hypercalcemia or hyperparathyroidism [190]. Most of the studies on mineral metabolism in dialysis patients have focused on HD but some recent studies demonstrate a similar risk in PD [191, 192]. There is currently no evidence that correction of abnormalities in mineral metabolism results in improvement in clinical outcomes of dialysis patients.

Table 2.4 Sources of infection of the peritoneal cavity in patients on peritoneal dialysis

Intraluminal
Touch contamination
Periluminal
Catheter-related infections (exit-site/tunnel infections)
Enteric
Iatrogenic (enteric, bacteremic, gynecologic)

Infectious Complications

Infectious complications, particularly peritonitis, have long been the proverbial “Achilles heel” of PD and have long accounted for technique failure [24, 106, 107] and catheter loss [23, 24, 193]. The pathophysiologic bases for peritonitis are summarized in Table 2.4.

As discussed earlier, refinements in connectology and use of the twin-bag systems have led to significant declines in the rates of peritonitis from touch contamination. Over the last decade, advances have been made in reducing catheter-related infections. The first step in preventing catheter-related infections is ensuring that the PD catheter is placed by an experienced operator under sterile conditions. The risk can be further reduced by using exit-site antibiotic prophylaxis by employing either mupirocin or gentamicin [194]. With these advances, the peritonitis rates have declined from about 1.4 episodes per patient-year to 0.5 episodes per patient-year in many centers [195, 196]. Guidelines for prevention, diagnosis, and treatment of infectious catheter-related complications were first published in 1983, have been revised several times, and are evidence based when evidence existed [196]. However, despite a bibliography of more than 9,000 publications on infections as a complication of peritoneal dialysis, the recommendations are hampered with insufficient randomized controlled trials to justify firm pronouncements on several topics being addressed. Therefore, they are not meant to be implemented in every situation. It is strongly advised that each center should examine its own pattern of infection, causative organisms, and sensitivities and adapt the protocols as necessary for local conditions. The guidelines can be considered as an important tool for quality improvement of peritoneal dialysis [197].

Peritoneal Sclerosis

Encapsulating peritoneal sclerosis (EPS) is a rare but life-threatening complication of peritoneal dialysis [198–201]. Most patients have undergone treatment at least 4 years, with the prevalence increasing with longer PD vintage [199]. The mortality rate is high, and in severe cases with complete intestinal obstruction, 60–93% of the patients die [199]. From experiences reported in the literature, optimal management requires a high index of suspicion for the diagnosis of the condition. Appropriate investigations include longitudinal peritoneal equilibration tests and regular measurement of CA125 in the dialysate. A sudden decrease in CA125 concentrations may indicate the development of EPS [202]. CT scanning of the abdomen for detecting fibrosis, thickening of the peritoneum, and calcifications may be helpful. There is no agreement about the therapy of choice for EPS, although it is generally agreed that total parenteral nutrition, steroids, and, sometimes, surgical enterolysis maybe important components [200]. Treatment of EPS with tamoxifen is still controversial [203]. The cause of EPS seems to be multifactorial. Given that only a small proportion of patients develop EPS, it is proposed that genetic factors may set up a predisposition for this life-threatening complication [204]. To address further research on this rare entity, international collaboration in the form of a global registry and DNA bank has recently been proposed [204].

Quality of Life

Studies on the outcome of dialysis treatment usually focus on mortality and morbidity. There is general consensus, however, that the quality of the remaining life is an important outcome parameter as well [205]. It is well known that quality of life (QoL) in new dialysis patients is substantially impaired, both in HD and PD patients [206–212]. In a study of 226 new dialysis patients (120 HD and 106 PD), it was observed that QoL is lower compared to the general population in all QoL dimensions [205]. Multivariate analysis showed that a higher number of co-morbid conditions, a lower hemoglobin level, and a lower RRF were the most important independent risk factors for a lower QoL.

However, these medical factors could explain only a small part of the variations in the observed QoL. Consistent with these observations, studies have shown that psychological and social issues have a significant impact on the QoL of PD patients [213–216]. Kutner et al. found limited evidence for an association between race and perceived health status and QoL in black and white patients starting dialysis (1,679 HD and 1,623 PD) enrolled in the DMMS Wave 2 cohort study [211].

It has been suggested that differences in QoL may become more apparent with increasing dialysis vintage. Longitudinal evaluation of the QoL was recently reported by Merkus et al. [206]. In 250 incident patients enrolled in the NECOSAD study, the physical QoL deteriorated during the first 18 months, both in HD and PD patients, but the deterioration was greater in PD patients. The mental QoL remained stable over time and did not differ between both dialysis modalities. These results are similar to the study by Wu et al. [212], but could not be confirmed by Kutner et al., who compared QoL in 455 HD and 413 PD patients [210]. PD patients' scores appeared to be higher than HD patients' scores with regards to the effects of kidney disease, burden of kidney disease, staff encouragement, and satisfaction with care.

When patients are confronted with the choice of dialysis modality, it is important to realize that there are distinct advantages and disadvantages to each of the modalities. Patients who initiate PD may be able to enjoy a period of time being largely independent of a dialysis facility, and they are more likely to be able to continue their jobs [217].

Future Directions

Over the past two decades, PD has established a niche for itself in the therapy of ESRD. Three different surveys – one each from United States, Canada, and the British Isles – concerning nephrologists' opinions about the optimal distribution of dialysis modalities reported that the optimal percentage of patients treated with PD should be around 30–40% [218–220]. When patients having no contraindication to PD are offered a free choice, 45–50% chose PD [69, 72]. These percentages are considerably higher than the 11% global PD penetration. Thus, much greater attention should be paid to optimal patient education. With the encouraging results with daily home HD, home therapies are likely to receive greater attention in the future. The effect of growth of home HD on the utilization of PD remains to be seen.

Economic Considerations

As discussed earlier, nonmedical factors are the most important determinant of choice of PD, and it is anticipated that these factors will continue to influence the use of this therapy. In the United States, annual costs for the HD patients are significantly higher than that for PD patients [57]. Greater utilization of self-care dialysis reduces overall costs: even after accounting for younger age and lower co-morbidity of the PD population; and annual per-capita Medicare expenditure is \$12,000 lower than for in-center HD [221]. With increasing costs of the Medicare ESRD program, this issue is likely to receive greater attention, with a possible push towards greater use of home dialysis.

On the other hand, in developing countries, efforts are underway to reduce the costs associated with PD therapy, particularly by reducing the need to import PDS from the developed countries. The greater the success at outsourcing the production of dialysis solutions, the greater would be the potential to lower the cost of therapy and, hence, the higher the probability of use of PD.

Quality Considerations

Efforts to further improve the outcome of PD, particularly to reduce the cardiovascular disease burden, should continue in the future. To achieve this goal we need evidence-based best practice guidelines like those being released by the International Society for Peritoneal Dialysis, Dialysis Outcomes Quality Initiative (DOQI), European Best Practice Guidelines, and Caring for Australians with Renal Impairment (CARI). It has been shown that the release of guidelines has some effect on clinical practice. Renal replacement therapy is being started in the United States at progressively higher levels of glomerular filtration rate [57]. In the Netherlands, the introduction of the DOQI guidelines resulted in a tendency towards earlier introduction of renal replacement therapy and higher doses of dialysis [222]. The only way to ensure that guidelines actually improve medical outcomes is to emphasize implementation strategies. Furthermore, guidelines should be systematically re-evaluated on their effectiveness in clinical settings.

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Nolph and Gokal's Textbook of Peritoneal Dialysis

Khanna, R.; Krediet, R.T. (Eds.)

2009, XII, 934 p., Hardcover

ISBN: 978-0-387-78939-2