AJKD
Core Curriculum in Nephrology

Update on Peritoneal Dialysis: Core Curriculum 2016

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Peritoneal dialysis (PD) is the major established form of renal replacement therapy that is performed primarily at home. Until recently, the prevalent rate of PD patients in the United States was declining, reaching a low of 6.9% in 2009. Since then, there has been a striking increase in PD use, with a prevalence rate of 9.7% in 2014. Consequently, since the original Core Curriculum on PD (from Teitelbaum and Burkart) was published in 2003, there has been a commensurate growth in information on the subject. This update focuses on relevant topics in the field, as outlined in Box 1.

EPIDEMIOLOGY

The number of patients treated with PD in the United States has been on the increase. This is largely due to the bundled payment system, which was introduced in 2011. PD is more cost-effective than in-center hemodialysis (HD), particularly after startup costs are absorbed. Comparing the first quarter of 2010 and the fourth quarter of 2012, prevalent counts of patients treated by PD increased by 24% (see PD prevalence in Fig 1); the corresponding increase in HD patients was only 9.6%. In the 2-year period before this, PD prevalence had remained essentially flat. PD incidence rates have also increased; between December 2010 and 2012, the PD incidence rate increased 22%, whereas the HD incidence rate decreased 2%. Declining overall dialysis rates may be due to improved care for chronic kidney disease, whereas higher PD use may be due to improved efforts in patient and provider education, as well as the mentioned economic incentives.

In 2011, total Medicare expenses for PD and HD patients increased 14.7% and 2.5%, respectively. Despite this, the per-patient expense remained lower for PD than HD, at $71,630 versus $87,945.

Additional Readings

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OUTCOMES IN PD

PD use in certain areas has markedly increased, and some concerns have risen about the suitability of candidates for PD therapy. One retrospective analysis examined technique survival and patient mortality in practices with high and low PD use. Neither practice setting experienced worse outcomes in technique survival. Larger samples will need to be studied to ensure that this is a fair assessment, but this initial finding is intriguing. In other retrospective cohorts, centers with larger numbers of PD patients under their care had more favorable peritonitis and transplantation rates and lower rates of transfer from PD to HD therapy. A large cohort in Canada of incident PD patients showed improved survival in more recent years (2001-2005 and 2006-2009) than in past years (1995-2000).

During 2012, annual mortality rates in PD and HD were similar, at 1.55 and 1.60 per 1,000 patients treated, respectively. This reflects a substantial improvement from 1993, when the mortality rate in PD (47%) was greater than that in HD (28%). Hospitalizations followed similar trends: PD patients were hospitalized at a rate of 1.61 per patient-year in 2012, a 21% improvement from 1985, and slightly better than HD patients (1.73 hospitalizations per patient-year during the same period). Several reasons have been postulated to explain these improvements, including better infection control and vascular access practices, use of cardioprotective medications and procedures, implementation of quality metrics, and changes in background population mortality rates.

Numerous retrospective studies have examined survival with PD versus in-center HD. It is unclear whether a distinct advantage of one modality truly exists. Canadian registry data from 1991 to 2007 showed a slight survival benefit for PD up to 18 months after dialysis therapy initiation and a benefit of HD after 36 months. A US cohort of incident dialysis patients from 2001 to 2004 showed 48% lower mortality in the PD group. A Finnish study of long-term dialysis patients from 2000 to 2009 demonstrated higher mortality among patients exclusively treated with PD versus HD. Australia and

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Box 1. Update on Peritoneal Dialysis

- Epidemiology
- Outcomes in peritoneal dialysis
- Peritoneal dialysis access
- Peritoneal dialysis solutions
  - Conventional solutions
  - Glucose-sparing solutions
    - Icodextrin
    - Amino acid
  - Neutral-pH, low-GDP solutions
- Adequacy of peritoneal dialysis
  - Concept of adequate dialysis
  - Adequacy
- Prescription options
- Volume management
- Complications
  - Infectious complications
    - Exit-site and tunnel infections
    - Peritonitis
  - Noninfectious complications
    - Peritoneal membrane changes
    - Ultrafiltration failure
    - Encapsulating peritoneal sclerosis
    - Future directions
- New frontiers
  - Urgent-start peritoneal dialysis
  - Peritoneal dialysis for AKI

Abbreviations: AKI, acute kidney injury; GDP, glucose degradation product.

New Zealand registry data showed increased cardiac mortality on Mondays for in-center HD patients, but no variation in patients treated with PD or home HD. Additionally, a Canadian study of more than 38,000 patients starting dialysis therapy between 2001 and 2008 found that in the 5 years after dialysis therapy initiation, risk for death was 20% higher in patients who started HD therapy with a central venous catheter (CVC), compared with those treated with PD. Patients starting HD therapy with an arteriovenous access had similar survival to the PD group. Survival in continuous ambulatory PD (CAPD) and automated PD was similar as well.

Registry data show that heart failure with preserved ejection fraction is common among patients treated with PD and leads to poor outcomes. A recent randomized trial looked at the use of spironolactone in 158 relatively new PD patients who also were receiving angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). The study, based in Japan, found that left ventricular mass index improved significantly in the spironolactone group versus the nontreatment group.

Based on data from the United States, cardiovascular and all-cause mortality has been found to be worse in patients with very low (<3.5 mEq/L) and very high potassium levels (>5.5 mEq/L). We do not have randomized trials to show that improved potassium levels will decrease mortality, but goals to normalize levels seem fitting.

Patients with diabetes treated with CAPD have worse survival and technique success than age-matched controls without diabetes. It also is very important to preserve residual kidney function (RKF) given its strong association with survival. Small randomized trials in prevalent PD patients using ACE inhibitors or ARBs have been shown to preserve RKF.

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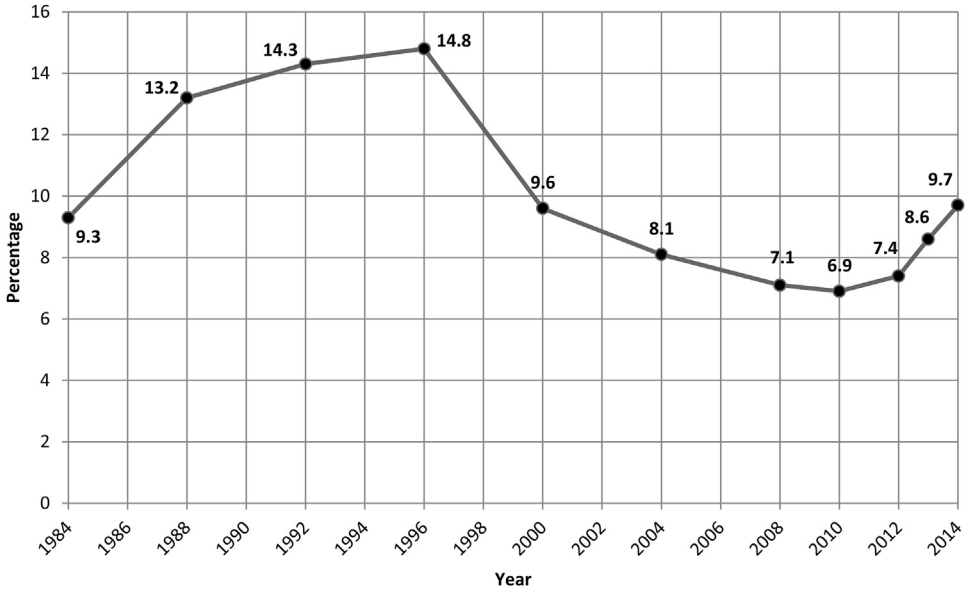

Figure 1. Prevalence of peritoneal dialysis in the United States: 1984-2014. Data from Watnick ("The State of Peritoneal Dialysis in the United States: From Inertia to Resurgence." Nephrology Self-Assessment Program. 2014;13(5):313).

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PD ACCESS

Obtaining an appropriate and well-functioning peritoneal access is critical to the success of PD treatment. Current catheters are constructed of silicone rubber. There are multiple catheter designs (Fig 2A) with different intraperitoneal configurations (straight or coiled), subcutaneous segments (straight or swan neck), and number of cuffs (1 or 2). The literature has not clearly demonstrated the superiority of one particular catheter design. A recent meta-analysis looking at removal rate and catheter survival of surgically inserted catheters favored catheters with a straight intraperitoneal segment. However, these results need to be interpreted with caution. Extended catheters are available for patients with an upper abdomen or presternal area exit site (Fig 2B). Use of these exit-site locations is valuable for patients with obesity, presence of ostomies, need for diapers, previous infections of an abdominal exit site, or urinary or fecal incontinence; patients who wish to use bathtubs or whirlpools could also benefit from an exit site of this kind. Of note, studies have suggested a lower risk for exit-site infections with upper abdomen or presternal area exit sites. However, the insertion technique for these extended catheters is more challenging and has been associated with rare mechanical complications specific to these catheters.

Appropriate preoperative planning is critical to minimize complications. Best practice guidelines are available for patient preparation, PD catheter insertion, and exit-site care. Preoperatively marking the abdominal exit site is crucial and should be done when the patient is dressed and in different positions. The exit site should be at least 2 cm from belt lines

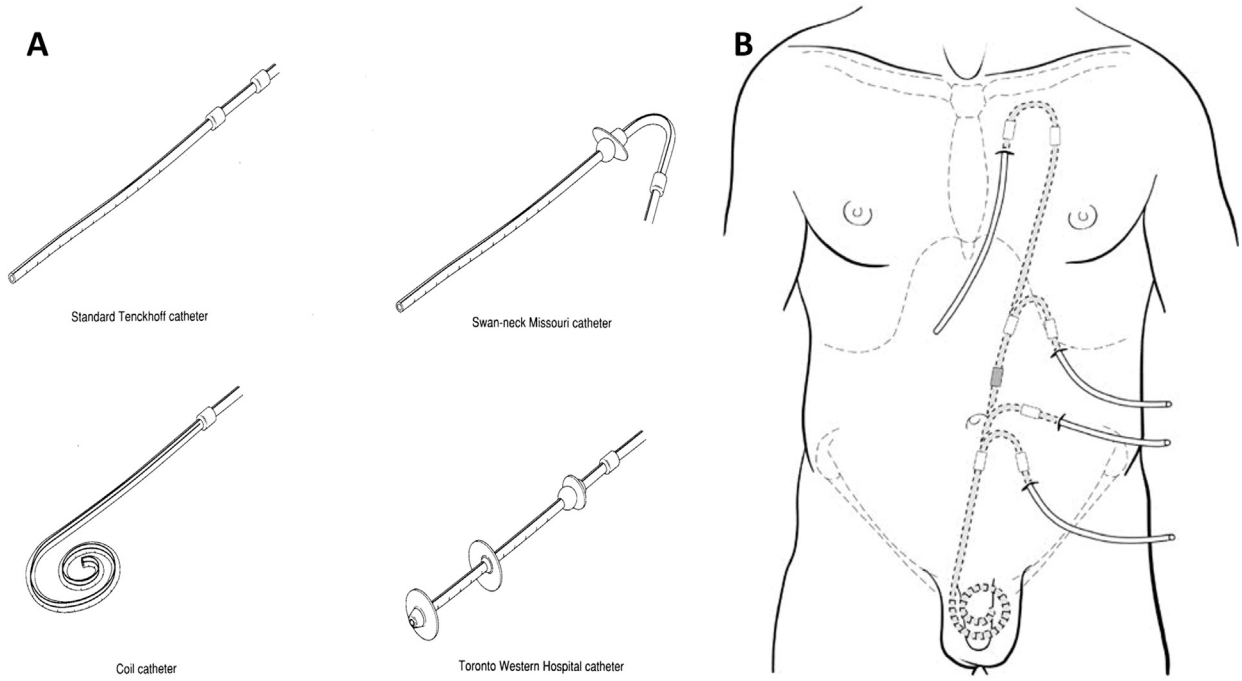

Figure 2. Peritoneal dialysis (PD) access. (A) Commonly used PD catheters, (B) variety of exit-site locations with the distal intraperitoneal segment in the pelvis. (A) Adapted from Gokal et al ("Peritoneal catheters and exit-site practices: toward optimum peritoneal access." *Perit Dial Int.* 1993;13:29-39) with permission of Multimed Inc. (B) Reproduced from Crabtree JH ("Selected best demonstrated practices in peritoneal dialysis access." *Kidney Int.* 2006;70:S27-S37) with permission of Nature Publishing Group.

and skin creases and folds and should be clearly visible to the patient so that he or she can perform daily exit-site care. The superficial cuff should also be 2 to 4 cm from the exit site.

There are multiple insertion techniques for placing a PD catheter: percutaneous, peritoneoscopic, open surgical dissection, and laparoscopic. Advanced laparoscopic PD catheter placement includes rectus sheath tunneling, selective prophylactic omentopexy, and/or adhesiolysis. The operator for PD catheter insertion can be a surgeon, interventional radiologist, or interventional nephrologist, depending on the procedure. Choice of operator and technique may depend on local expertise, operator availability, urgency of the clinical situation, and patient factors (past abdominal surgeries, hernias, comorbid conditions, or anesthesia risk). Outcomes of the different insertion techniques are generally favorable and depend on the expertise of the operator/center. Although laparoscopic placement is associated with longer surgical times, higher costs, and the need for general anesthesia, it can proactively address problems that may adversely affect catheter outcomes and is associated with excellent long-term outcomes.

PD catheter embedment should be considered in patients who have selected PD therapy in advance of anticipated need. The external segment of the catheter is buried in the subcutaneous space instead of being brought to the surface. When the decision to initiate PD therapy is made, the external segment of the catheter is externalized through a small incision and full-volume PD can be started. In a recent study, 85.7% of catheters functioned immediately, and including those undergoing laparoscopic revision, 98.8% were successfully used for PD. Placement of an embedded catheter can reduce the stress in obtaining PD access when dialysis is urgently needed and also could help prevent HD therapy initiation with a CVC.

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PD SOLUTIONS

Conventional Solutions

A variety of PD solutions are available for clinical use (Table 1). The composition of PD solutions is broadly divided into the osmotic agent, buffer, and electrolytes. The electrolyte composition of all PD solutions varies slightly by manufacturer (sodium concentration, 132-134 mmol/L; calcium concentration, 1.25-1.75 mmol/L; and magnesium concentration, 0.25-0.75 mmol/L). Dextrose is the osmotic agent used in conventional PD solutions and is available in 3 concentrations: 1.5%, 2.5%, and 4.25% (as glucose monohydrate). Heat sterilization of glucose leads to the generation of glucose degradation products (GDPs). Because fewer GDPs are generated when this heat

Table 1. PD Solution Formulations

PD Solution	Osmotic Agent	Osm, mOsm/L	pH	No. of Chambers	Lactate, mmol/L	Bicarbonate, mmol/L	GDP Content
Conventional							
Dextrose based (various manufacturers)	Glucose	345-484	5.5	1	35-40	0	High
Glucose sparing							
Extraneal (Baxter)	Icodextrin	282-286	5.5	1	40	0	Low
Nutrineal (Baxter)	Amino acids	365	6.5	1	40	0	Low
Neutral pH, low GDP							
Balance (FMC)	Glucose	358-511	7.0	2	35	2.5	Low
BicaVera (FMC)	Glucose	358-511	7.4	2	0	34	Low
Gambrosol Trio (Gambro)	Glucose	357-483	6.3	3	40	0	Low
Physioneal (Baxter)	Glucose	344-583	7.4	2	10 or 15	25	Medium

Note: Data from Cho and Johnson (*Curr Opin Nephrol Hypertens.* 2014;23:192-197), Heimburger and Blake ("Apparatus for Peritoneal Dialysis," in *Handbook of Dialysis.* 5th ed. Lippincott, Williams & Wilkins; 2015:408-414), and Perl et al (*Kidney Int.* 2011;79:814-824).

Abbreviations: GDP, glucose degradation product; Osm, osmolality; PD, peritoneal dialysis.

sterilization occurs at a low pH, conventional PD solutions use lactate as a buffer and have a pH of ~5.5. A single-bag system limits the use of bicarbonate as the buffer because this may lead to calcium and magnesium precipitation.

There is now evidence that these conventional PD solutions are associated with both local and systemic toxicities. Factors that contribute to these toxicities include exposure to the low pH, lactate buffer, hyperosmolality, glucose as the osmotic agent, and GDP concentrations. Local toxicities can range from inflow pain to chronic changes that occur to the peritoneal membrane, which can lead to loss of peritoneal membrane function, encapsulating peritoneal sclerosis (EPS), and technique failure. Systemic effects of glucose absorption are associated with hyperglycemia, hyperinsulinemia, hyperlipidemia, and weight gain, all of which can contribute to increased cardiovascular morbidity. In addition, the generation of GDPs can not only cause local toxicity, but may also lead to loss of RKF. New PD solutions have been developed with the goal of attenuating some of these adverse toxicities; these are broadly classified as glucose-sparing solutions with neutral pH and low GDP (1).

Glucose-Sparing Solutions

Icodextrin

Concerns regarding the local and systemic adverse effects of glucose, as well as its limitation as an effective osmotic agent (especially in high transporters), have led to the development of alternative agents to induce ultrafiltration. Icodextrin, a polyglucose solution that induces ultrafiltration by an oncotic effect, is available and widely used in the United States. Icodextrin solutions for PD therapy are isosmotic and have a low GDP content. Absorption of icodextrin is much slower than that of glucose, and ultrafiltration increases throughout the length of exposure. This is useful for the daytime dwell in continuous cyclic PD (CCPD) or the long overnight dwell in CAPD. Icodextrin use is associated with increased levels of maltose, maltotriose, and other oligopolysaccharides and has been associated with an increased incidence of cutaneous reactions. Icodextrin and maltose can interfere with or cause false elevations in glucose readings, so patients must be instructed to use a glucometer compatible with icodextrin use.

Many studies have investigated the benefits of using icodextrin for the long dwell of the day but conventional PD solutions for the remainder of the PD prescription (which, incidentally, may confound results of studies on long-term outcomes). In the Improved Metabolic Control of Physioneal, Extraneal, Nutrineal versus Dianeal only in Diabetic Continuous Ambulatory Peritoneal Dialysis and Automated Peritoneal Dialysis Patients (IMPENDIA) and the Evaluation of Dianeal, Extraneal and Nutrineal versus Dianeal only in Diabetic CAPD Patients (EDEN) trials, patients assigned to the invention group received one exchange per day of amino acid solution and one exchange with icodextrin (for the long dwell) in addition to glucose-based PD solutions. The control group received glucose-based PD solutions exclusively. Trials showed improvements in levels of apolipoprotein B, glycated hemoglobin, serum triglycerides, and very low-density lipoprotein cholesterol in the intervention group compared with controls. However, the total number of adverse events was higher in the intervention group. A recent Cochrane analysis found that icodextrin is associated with a significant reduction in uncontrolled fluid overload and improvement in peritoneal ultrafiltration in comparison to conventional glucose solutions for PD therapy. Moreover, icodextrin use was not observed to compromise RKF and urine output. Some small studies have also suggested that icodextrin use may be associated with improved patient and technique survival, but these outcomes were not confirmed by the Cochrane analysis. Further, one study suggested that use of the osmotic agent in anuric patients receiving automated PD is associated with a lower rate of loss of membrane function.

In summary, icodextrin is a glucose-sparing PD solution that has been associated with improvements in glycemic control, glucose-induced lipid abnormalities, and ultrafiltration.

Amino Acid

Although amino acid–based PD solutions are glucose sparing, they are used primarily in nutritionally compromised patients. Such solutions contain 1.1% amino acids and have osmolality similar to the 1.5% dextrose solutions used as a daily exchange. Studies documenting the long-term efficacy of 1.1% amino acid solutions have been controversial. Worsening of acidosis and an increase in serum urea nitrogen level can be associated with their use.

Neutral-pH/Low-GDP Solutions

Developing PD solutions with a neutral pH and low GDP content is an alternative strategy for minimizing toxicity in PD therapy that occurs as a consequence of conventional glucose solutions. These new solutions use a 2- or 3-compartment solution bag. In one compartment, the glucose is heat sterilized at a very low pH, which reduces the formation of GDPs. The other compartment(s) contain the buffer (lactate, bicarbonate, or both) and electrolytes at an alkaline pH. Before use, the compartments are mixed, resulting in a neutral pH. There are 4 products on the market based on this strategy (Table 1), but none are currently available in the United States.

Many studies have examined whether these new solutions improve outcomes. In the past 2 years, there have been 3 systematic reviews of randomized controlled trials (RCTs) comparing the effect of biocompatible PD solutions on various clinical outcomes. Each review noted that the investigations in question are in general of poor quality. The reviews also noted that the studies were limited by high dropout rates and included patients with varied dialysis vintages. Icodextrin use was allowed in many of the included studies; the type of biocompatible solution used varied. In studies with more than 12 months of follow-up, use of neutral-pH low-GDP solutions was associated with greater urine volumes and improved preservation of RKF. There was no significant effect on peritonitis, technique failure, or adverse events, but there was a trend toward a decreased incidence of inflow pain. With 185 patients, the balANZ trial was the largest of the RCTs that included only incident patients. It showed the beneficial effects of neutral-pH low GDP solutions on RKF, as well as longer time to first peritonitis episode and lower peritonitis rates. (Unfortunately, these results were not confirmed by the 3 systematic reviews.) The balANZ trial also demonstrated stable peritoneal solute transport rates over 24 months, whereas such rates in the control group progressively increased. In countries where these solutions are available, the potential benefits need to be weighed against increased cost.

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ADEQUACY OF PD

In 2006, the International Society of PD (ISPD) published clinical practice guidelines for the adequacy of solute and fluid removal for PD. The general principles in these guidelines continue to steer our therapies.

Concept of Adequate Dialysis

Often, adequacy of dialysis is considered a numerical concept in nephrology, namely measured urea removal by a combination of a patient's peritoneal membrane and RKF. However, an adequate dialysis treatment should deliver therapy that attains an adequate quality of life for patients. Quality of life in dialysis can include multiple measurable parameters, such as nutrition, anemia management, presence or absence of mineral and bone disorders, acid-base balance, mental health, and hope for future well-being (eg, whether kidney transplantation can be an option). All these parameters should be regularly addressed in the PD patient.

Adequacy

When total-solute clearance is used to assess adequacy, one measure employed is weekly Kt/V_{urea}, a unitless measure of clearance distributed over total-body water per unit of time. Peritoneal Kt/V_{urea} and residual kidney Kt/V_{urea} are summed to determine total weekly Kt/V_{urea}, although the simple addition of these 2 values has not been validated scientifically. Both urine and peritoneal fluid volumes are collected at regular intervals and can be determined more frequently when there are changes in clinical status or the PD prescription.

Based on results of clinical studies performed over the last 15 years, delivered weekly clearance should be a minimum Kt/V_{urea} of 1.7, combining peritoneal and kidney clearances. The ADEMEX (Adequacy of PD in Mexico) trial was an RCT of 965 patients that compared doses of 47 or 60 L/wk/1.73 m^2 of creatinine clearance, equivalent to Kt/V_{urea} of approximately 1.7 or 2.0 per week. RKF was similar in both groups. Patient survival was similar even after multivariable adjustments. A trial from Hong Kong randomly assigned 320 incident patients to 3 groups: $Kt/V_{urea} > 2.0$, 1.7 to 2.0, or 1.5 to 1.7 per week. Survival was similar in all 3 groups, but patients in the lowest Kt/V_{urea} group required more erythropoietin and had more uremic symptoms. In retrospective studies, patients experience poorer technique survival at the lowest Kt/V_{urea}.

Of note, some patients may exhibit signs of underdialysis despite $Kt/V_{urea} > 1.7$. If there are no obvious correctable reasons, PD can be intensified further.

PRESCRIPTION OPTIONS

To reach these goals, the PD prescription is usually initiated as 1 of 3 modalities. With CAPD therapy,

patients perform 4 manual exchanges per day at the start of treatment. With CCPD, patients can program the cycler to perform multiple exchanges overnight for a predetermined period, and the cycler machine will perform a final fill before the patient disconnects in the morning. Alternatively, the machine can be programmed to not perform a final fill, which leads to no peritoneal clearance during the daytime, a treatment termed nocturnal intermittent PD. With tidal PD therapy, the cycler machine performs an initial fill, and small volumes of dialysis fluids are instilled repeatedly overnight. There is minimal evidence that any modality is clearly superior, though the cycler machine minimizes the number of times that a patient disrupts the sterile connection between the PD catheter and instilled dialysis fluids. Some physicians consider an incremental approach at the time of PD therapy initiation to minimize dextrose exposure. These prescriptions often use smaller exchanges or fewer exchanges per day when a patient has substantial RKF.

The prescription for all modalities can either be initiated empirically or modeled with a computer program using patient-level data. Adjustments are often made after calculating dialysis adequacy in 2 to 4 weeks after initiation. A peritoneal equilibration test can be performed 4 weeks after the PD therapy initiation date to assess peritoneal membrane characteristics. This test will categorize patients into one of 4 groups (high, high average, low average, and low) and allows the prescriber to further refine the dialysis prescription. As also described in the 2003 Core Curriculum article by Teitelbaum and Burkart, the standard protocol for a peritoneal equilibrium test is as follows:

1. Perform in morning after complete drain of the prior dwell (typically >8 hours if CAPD).
2. Instill usual fill volume using 2.5% dextrose dialysate.
3. Sample dialysate immediately after infusion and at 2 and 4 hours to determine creatinine, urea, and glucose concentrations.
4. Sample blood at 2 hours after dialysate infusion to determine creatinine, urea, and glucose levels.
5. Drain dialysate at 4 hours and record drain volume.
6. Calculate dialysate to plasma (D/P) ratios for creatinine and urea at 2 and 4 hours. Calculate the ratio of dialysate glucose and compare to the initial concentration (D/Do) at 2 and 4 hours.
7. Plot these on the standard peritoneal equilibrium test graphs to determine peritoneal membrane type (Fig 3).

PD requires a significant time commitment and attention to detail by patients. Many factors contribute to the patient's capacity to maintain PD. Patient burnout and loss of functional capacity are not uncommon and are potential reasons for transitioning from PD to HD therapy.

Assisted PD relies on family members or health care providers to help patients continue PD therapy. Recent studies have shown that assisted PD can provide some success in preventing modality transfers. In one (albeit not randomized) study, 21% of self-care patients but only 15% of assisted patients transitioned to HD therapy after 2 years.

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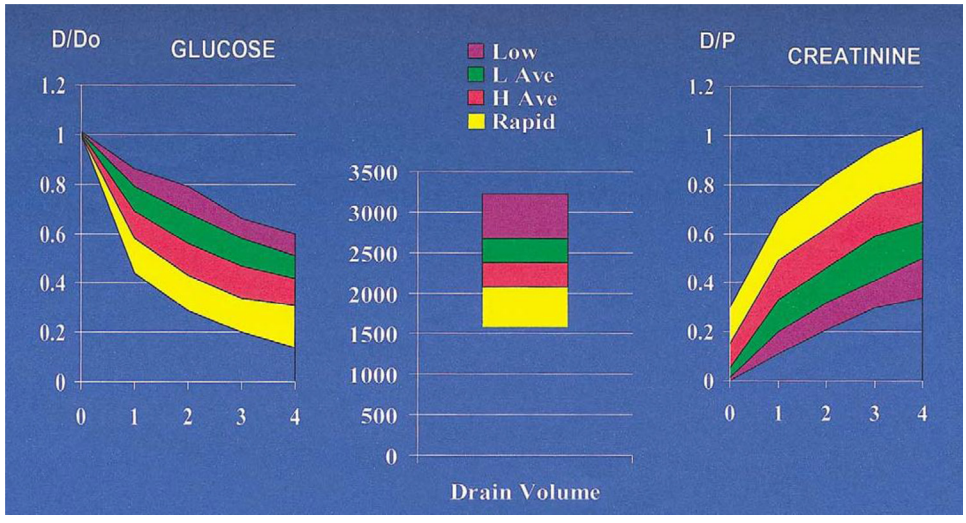

Figure 3. Peritoneal equilibrium test (PET). Adapted from Teitlbaum and Burkhart ("Peritoneal dialysis." *Am J Kidney Dis.* 2003;42(5):1082-1096) with permission of Elsevier. D/Do, dialysate glucose concentration at indicated time/dialysate glucose concentration at time 0; D/P, dialysate to plasma.

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VOLUME MANAGEMENT

Maintenance of euvolemia is one of the key goals of caring for patients treated with PD. The approach to volume management is multifaceted. Adherence to a sodium-restricted diet is critical, and dietary education should be part of each patient's care plan. RKF not only is associated with better outcomes, but also helps maintain extracellular volume. Strategies to preserve RKF (ACE-inhibitor/ARB therapy and avoiding nephrotoxins, hypovolemia, and peritonitis) should be pursued. High-dose loop diuretics can be used to augment urine output, but it is unclear whether this strategy is superior to modulation of PD ultrafiltration. There is some observational data by Medcalf et al suggesting that high-dose loop diuretics may preserve RKF, but it is unknown if this method also has deleterious effects on RKF.

PD ultrafiltration becomes increasingly important as RKF declines and can be modified by adjusting the type of PD solution used. Increasing the strength of the dextrose solution can enhance ultrafiltration by increasing the osmotic gradient. Understanding the patient's transport characteristics, as determined by the peritoneal equilibrium test, helps guide the PD prescription. High to high-average transporters are at risk for inadequate ultrafiltration due to more rapid glucose absorption and thus dissipation of the osmotic gradient. High transporters benefit from shorter dwell times and icodextrin use for the long dwell of the day to induce ultrafiltration.

In addition to checking adherence to dietary recommendations in a patient with volume overload, health care providers should evaluate adherence to the PD prescription and consider appropriate dialysate selection. In patients treated with PD, peritoneal membrane structure and transport characteristics change over time and need to be monitored. The PD prescription and transport status should be reevaluated, and adjustments based on these studies should be made. Strategies to reduce episodes of peritonitis and minimize dextrose exposure may help preserve peritoneal membrane function. Patients with poor ultrafiltration should be evaluated for constipation, catheter dysfunction, and leaks. If volume overload persists after evaluation of these issues and prescription optimization, the patient should be assessed for ultrafiltration failure (see Noninfectious Complication section).

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COMPLICATIONS

Infectious Complications

Infectious complications from PD result in substantial morbidity and mortality. Fewer than 4% of peritonitis episodes result in death, but 15% to 18% of patients treated with PD die as a result of peritonitis. Peritonitis also can lead to membrane failure, which can cause technique failure. Thus, prevention and appropriate treatment of peritonitis is critical for patient well-being and successful provision of PD. Two large databases from Scotland and Australia show peritonitis rates of 0.6 episodes per year at risk; however, rates vary widely for unclear reasons. Approximately 20% of infections are catheter related.

Exit-Site and Tunnel Infections

A reduction in exit-site infections results in a reduction in peritonitis. Therefore, preventing exit-site infections is appropriate for reducing peritonitis rates. Mupirocin and gentamicin have been used for daily exit-site care to prevent infections. Mupirocin is effective against *Staphylococcus aureus* but not *Pseudomonas aeruginosa*, both of which can cause peritonitis through infection at the PD catheter exit site. Also, there are reports of *S aureus* resistance to mupirocin. One randomized trial showed the superiority of gentamicin over mupirocin in preventing exit-site infections; subsequent retrospective trials showed equivalent results between the 2 agents. A recent randomized trial comparing peritonitis rates in patients using ointment containing either mupirocin

or a polysporin triple compound showed no difference in catheter-related infections, though the polysporin group had an unacceptable rate of fungal peritonitis.

Purulent drainage from an exit site indicates the presence of infection. Erythema at the interface of the catheter and the skin may or may not represent infection, depending on the clinical situation; erythema at the exit site with a diameter $>$ 14 mm is usually of concern for infection.

A tunnel infection can present with erythema, edema, or tenderness over the subcutaneous pathway of the PD catheter, but may also have no outwardly detectable signs. Ultrasonographic evidence is the gold standard for diagnosis.

Empirical therapy should always cover *S aureus*, with the most concerning organisms being *S aureus* and *Pseudomonas* species. Exit-site and tunnel infections with these organisms can lead to peritonitis and must be treated aggressively. Oral antibiotics are as effective as intraperitoneal injection and are generally appropriate unless methicillin-resistant *S aureus* is present. Empirical therapy can be initiated immediately to cover Gram-positive organisms at a minimum. A penicillinase-resistant or first-generation cephalosporin is frequently used. The care team can also wait for culture results to direct the choice of antibiotic therapy. The 2010 ISPD guideline update for PD-related infections provides advice on the appropriate choice of antibiotics (Table 2).

The minimum treatment length is 2 weeks or until the exit site appears normal. Beyond 3 weeks, catheter replacement can be considered. Occult tunnel infections also could be present, so ultrasonographic investigation may be appropriate as the infection resolves. Exit-site and tunnel infections that result in peritonitis often require catheter removal and replacement, as well as creation of a new exit site.

Peritonitis

Peritonitis can occur without cloudy effluent and can present with other symptoms, such as abdominal pain, fever, constipation, and diarrhea. Likewise, cloudy effluent does not necessarily indicate infectious peritonitis. Nevertheless, patients presenting with cloudy effluent should be presumed to have peritonitis, which is confirmed by a cell count, blood differential test, and blood culture of the peritoneal fluid. An effluent white blood cell count of 100/μL after a 2-hour dwell with at least 50% neutrophilic cells indicates inflammation, with peritonitis as the most likely cause.

Initiating empiric therapy to cover Gram-positive and Gram-negative bacteria is important because these organisms account for 60% to 70% and 15% to 25% of infections, respectively. No organisms are found in up to 15% of peritonitis cases, and fungi cause 2% to 3% of episodes. Polymicrobial peritonitis should lead to investigation for intra-abdominal catastrophes, including pancreatitis and ruptured viscus. Subsequent culture results and sensitivities can guide and narrow antimicrobial therapy. Serious consequences of peritonitis (relapse, technique failure, and death) are more likely to occur if treatment is deferred.

Guidelines from the ISPD offer a thoughtful approach to therapy. First- and third-generation cephalosporins are typically used for empiric coverage unless the patient had prior infections with resistance to first-generation cephalosporins or the institution has high rates of resistance to them. In either case, vancomycin can be used with a third-generation cephalosporin. Patients with minimal RKF (defined as urine

Table 2. Intraperitoneal Antibiotic Choices for Peritonitis

Gram Stain Results	Therapy: Typical Initial Agents	Examples: Dosing for CAPD, per Exchange, Once Daily[a]	Examples: Dosing for Automated PD Once Daily, Long Dwell[b]
Gram-positive	First-generation cephalosporin	Cefazolin 15 mg/kg	Cefazolin 20 mg/kg
		Vancomycin 15-30 mg/kg every 5-7 d; aim for trough $>$ 15 μg/mL	Vancomycin loading dose of 30 mg/kg, then 15 mg/kg every 3-5 d; aim for trough $>$ 15 μg/mL
Gram-negative	Third-generation cephalosporin or quinolone; aminoglycoside can be used if urine output $<$ 100 mL/d	Ceftazadime 1,000-1,500 mg	Ceftazadime 1,000-1,500 mg
		Gentamicin/tobramycin 0.6 mg/kg	Gentamicin/tobramycin loading dose 1.5 mg/kg, then 0.5 mg/kg
Organisms not seen	Cover Gram-positive and -negative organisms		

Abbreviations: CAPD, continuous ambulatory peritoneal dialysis; ISPD, International Society for Peritoneal Dialysis; PD, peritoneal dialysis.

[a]Refer to Table 4, ISPD Guidelines/Recommendations, *Perit Dial Int.* 2010;30:393-423 for continuous CAPD dosing.

[b]Refer to Table 5, ISPD Guidelines/Recommendations, *Perit Dial Int.* 2010;30:393-423 for additional antibiotic dosing.

output < 100 mL/d) can use aminoglycosides. Intraperitoneal administration is recommended unless the patient is hospitalized and acutely ill. Then, intravenous administration should be considered. The treatment course should be continued for 2 weeks, except in the case of *S aureus*, *Enterococcus* species, *Psuedomonas/Stenotrophomonas* species, or multiorganism peritonitis, which require 3 weeks of therapy. If no organisms are found, Gram-negative coverage can be discontinued at 96 hours if the patient is clinically improving, and Gram-positive coverage can continue for a total of 2 weeks. Treatment of fungal infections usually fails, and early catheter removal is a prudent way to proceed. Given the poor outcomes with fungal peritonitis, the use of fungal prophylaxis has been advocated, particularly in centers with high rates of fungal peritonitis. Several studies have shown benefit with agents such as nystatin and fluconazole administered during antibiotic use for bacterial peritonitis, although this has not been a uniform finding. In the case of relapsing peritonitis, defined as the recurrence of peritonitis due to the same organism within 4 weeks of therapy completion, catheter removal should be considered. Alternatively, for infections with Gram-positive organisms, another therapy course can be attempted.

Novel techniques are in development for earlier detection of peritonitis, but these techniques are not yet recommended for general use. The presence of bacterial DNA fragments may be a predictor of relapse and could serve an important role in peritonitis episodes caused by infections with high relapse rates, such as those due to *S aureus* and *P aeruginosa*. One study showed that patients who experience relapse have high rates of these DNA fragments 5 days before and the day of antibiotic course completion (however, these fragments were not indicative of active infection). These findings suggests that high levels of DNA fragments can be used to alter treatment strategies, but it must be noted that the study was in a single center with a small sample size and needs to be replicated before its recommendations are universally adopted.

Randomized trials comparing icodextrin- to glucose-based solutions show similar peritonitis risks. The newer solutions with bicarbonate or lactate as a buffer, more neutral pH, and fewer or no GDPs are potentially more biocompatible and could improve peritonitis rates. One RCT showed lower rates of peritonitis (0.30 vs 0.49 episodes per year) comparing biocompatible with traditional solutions. However, 2 systematic reviews that included observational trials did not show a difference between these solutions.

Facilities should follow their peritonitis rates and consider quality improvement programs if their rates are high or substantially increase over time.

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Noninfectious Complications

The noninfectious complications associated with PD can be subdivided into mechanical, metabolic, and those related to changes to the peritoneal membrane during long-term PD therapy. This section focuses on the complications associated with alterations in the peritoneal membrane: ultrafiltration failure and EPS.

Peritoneal Membrane Changes

Long-term PD therapy has been associated with both morphologic and functional changes in the peritoneum. Structural changes include loss of mesothelial integrity, submesothelial fibrosis, and a hyalinizing vasculopathy (Fig 4). The potential causative factors are likely multifactorial and include the PD catheter, a component of the dialysate (low pH, glucose exposure, hyperosmolality, GDPs, and lactate), inflammation, systemic factors, and

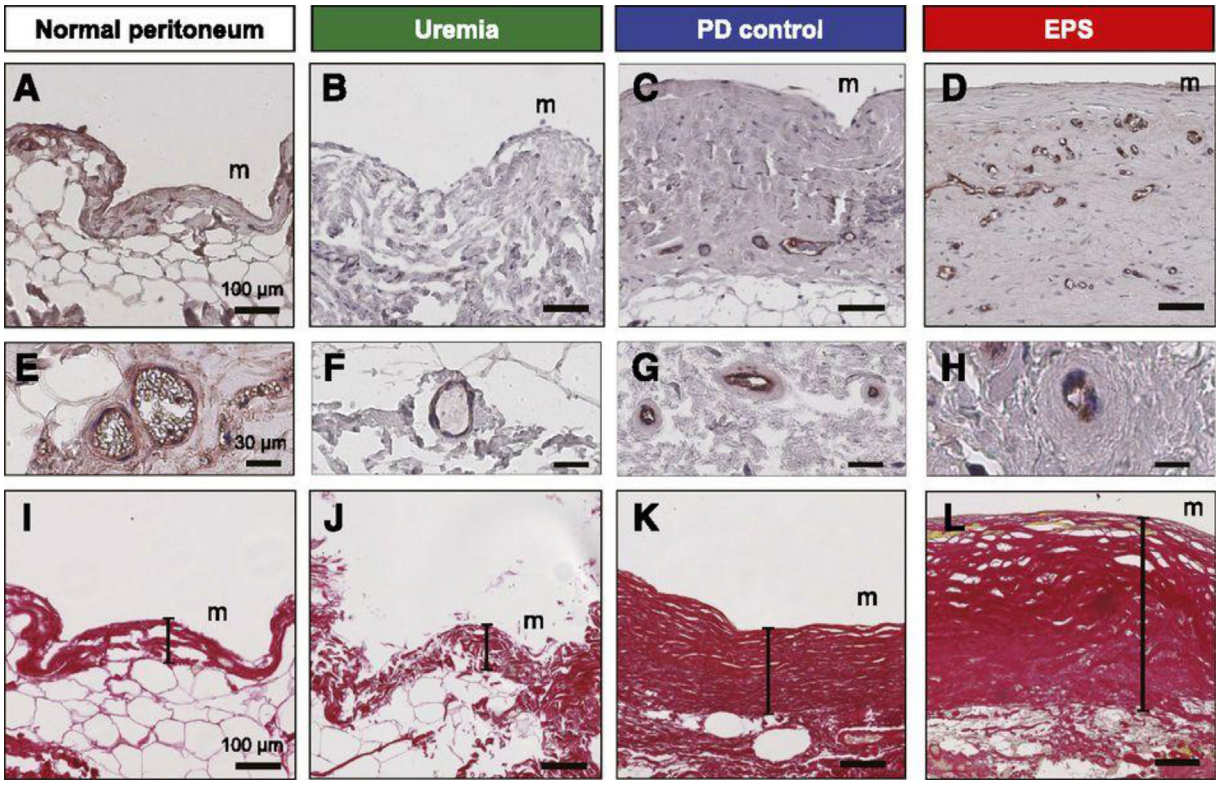

Figure 4. The peritoneum in encapsulating peritoneal sclerosis (EPS) is characterized by an excessive vascular and fibrotic response to peritoneal dialysis (PD). (A-D) Immunostaining for von Willebrand factor in (A) normal, (B) uremic, (C) control PD, and (D) EPS peritoneum reveals progressive vascular proliferation from A to D. (E-H) Representative peritoneal sections show the extent of vasculopathy by staining for von Willebrand factor in the postcapillary venules in (E) normal, (F) uremic, (G) control PD, and (H) EPS peritoneum. Long-term exposure to PD and EPS both associate with thickening of the capillary wall in venules with a 25- to 50-μm diameter. (I-L) Representative sections of parietal peritoneum from (I) normal, (J) uremic, (K) control PD, and (L) EPS peritoneum stained with picrosirius red. Submesothelial thickness (denoted by the bar extending from the mesothelial surface to the upper limit of the adipose tissue) significantly increases from I to L. Adapted with permission from Morelle et al [published online ahead of print January 30, 2015]. *J Am Soc Nephrol*. http://dx.doi.org/10.1681/ASN.2014090939).

potentially a genetic predisposition. These factors lead to the generation of cytokines and cellular changes that ultimately progress to fibrosis and neoangiogenesis. Investigation of peritoneal effluent biomarkers and the molecular pathways involved in the inflammatory and fibrosing processes that occur during long-term PD therapy are areas of active research.

Ultrafiltration Failure

The mentioned structural changes to the peritoneum may be associated with functional changes in some patients treated with long-term PD therapy. An increase in transport rate for small solutes (increase in the D/P creatinine ratio) and a decrease in the osmotic conductance (efficiency of ultrafiltration given a particular osmotic gradient) may occur and has been associated with dextrose exposure. This may lead to ultrafiltration failure, which is defined as fluid overload in association with ultrafiltration volume < 400 mL using a modified peritoneal equilibrium test (similar to the standard test but performed using a 4.25% dextrose exchange to create a greater osmotic gradient). Most patients who experience ultrafiltration failure are high transporters, and these cases are termed type I ultrafiltration failure (UFF). If optimization of the PD prescription and use of icodextrin fails to improve volume status, the patient may need to be transferred to HD therapy. Deficient aquaporin function and excessive lymphatic reabsorption (type III UFF) are additional causes of ultrafiltration failure. Much less common is a patient with UFF and low transport status (type II UFF), which usually reflects a decrease in membrane surface area. Peritonitis can lead to membrane damage and type I UFF in the short term, a condition reversible with resolution of peritonitis. If peritonitis results in adhesions and fibrosis, it can cause type II UFF.

Encapsulating Peritoneal Sclerosis

EPS is a rare but serious complication of PD. Epidemiologic studies reveal that the overall incidence of EPS ranges from 0.5% to 4.4%, but this rate increases with length of PD treatment. Thus, the incidence of EPS is 2.1% to 6.4% at 5 years and 5.9% to

19.4% at 8 years of PD treatment. However, EPS may present after PD therapy has been discontinued. EPS is associated with significant morbidity and mortality (18%-67%). In addition to time on PD therapy, other risk factors include high glucose exposure, younger age, ultrafiltration failure, kidney transplantation, chemical exposure, inflammation/peritonitis, discontinuation of PD therapy, and genetic predisposition.

The diagnosis requires both clinical features *and* evidence of bowel encapsulation either radiologically or pathologically. Clinical manifestations of EPS include symptoms associated with bowel obstruction, hemoperitoneum, presence of an abdominal mass, and malnutrition/failure to thrive. In addition, acquired ultrafiltration failure and high transport status may occur. Computed tomographic scanning is recommended as the initial imaging procedure for the radiologic diagnosis of EPS. Two computed tomographic scoring systems have been defined with good sensitivity and specificity; both systems are based on peritoneal thickening, peritoneal calcification, evidence of bowel adhesion/obstruction, and the presence of loculated fluid (Fig 5). It should be emphasized that EPS cannot be defined by findings on computed tomography in the absence of clinical symptoms. The pathologic features of EPS (Fig 4) include mesothelial denudation, interstitial fibrosis, and vasculopathy, which are similar to features accompanying ultrafiltration failure and changes associated with long-term PD treatment. Investigations attempting to discriminate patients with chronic membrane changes, ultrafiltration, or EPS have been inconsistent or nonspecific. These have included pathologic findings and various biomarkers. However, a decline in free-water transport appears to be a predictor of EPS.

Given that the pathophysiologic processes and changes that may occur with long-term PD therapy are similar to those associated with EPS (and most individuals do not develop EPS), a 2-hit hypothesis for the pathogenesis of EPS has been suggested. The "second hit" triggers fibrosis, bowel encapsulation, and the clinical symptoms. In theory, the second hit could be any combination of the mentioned risk factors for EPS.

Management of EPS can be viewed as supportive (eg, nutrition), medicinal, and surgical. In general, the PD catheter is removed after EPS diagnosis. However, there may be some beneficial effects of regular peritoneal lavage by removing the mediators of the fibrotic process (which may account for the diagnosis of EPS only after PD therapy is discontinued). Evaluation of medical

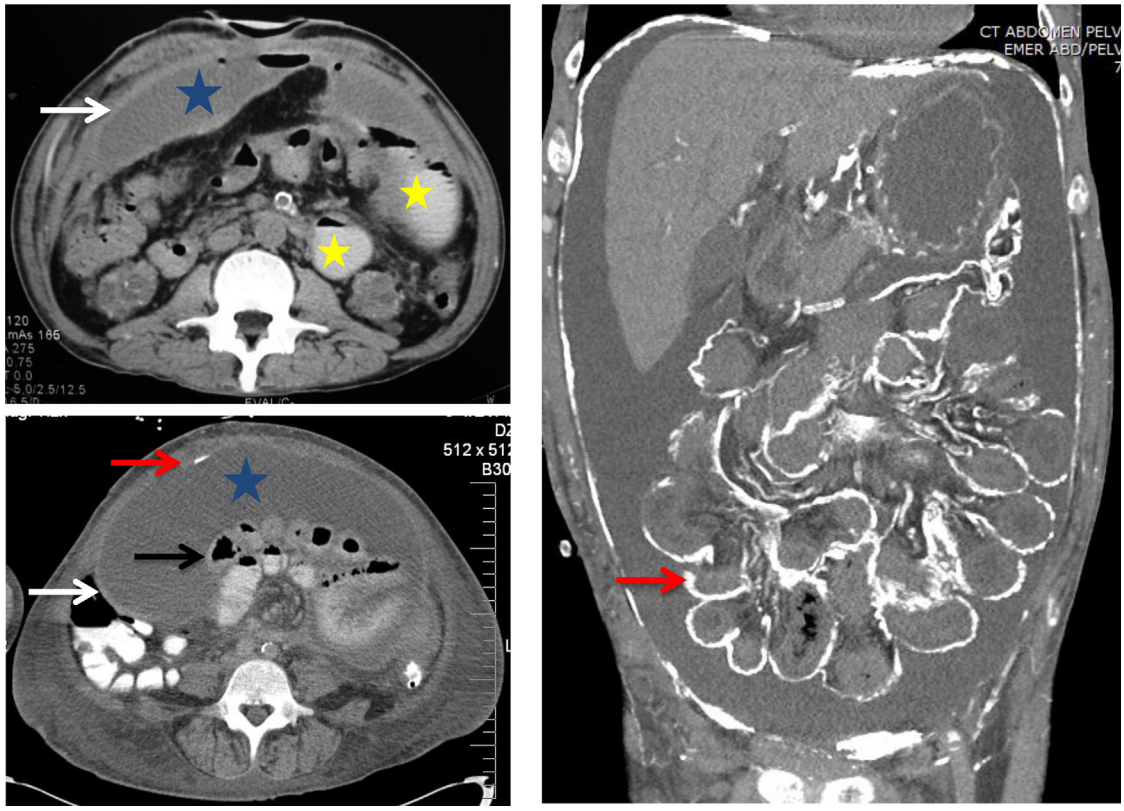

Figure 5. Characteristic computed tomographic findings of encapsulating peritoneal sclerosis: peritoneal thickening (white arrow), peritoneal calcification (red arrow); loculated fluid collection (blue star), dilated loops of bowel (yellow star), and tethered small bowel loops (black arrow). Top and bottom left panels courtesy of Dr S.F. Cameron.

treatments for EPS is limited by the lack of RCTs; the available data are primarily from case series. Immunosuppressants to dampen inflammation and tamoxifen (for its antifibrotic properties) have been used to treat EPS, with some series demonstrating promising results. Surgery is indicated for nonresolving obstructive symptoms or perforation. Improved outcomes have been demonstrated with specialized referral centers and improved surgical techniques.

Given the risk for EPS, what do we tell our patients considering long-term PD therapy? As noted, only a small percentage of patients who start PD therapy will develop EPS, and the risk increases with time treated with PD. It is difficult to predict who will develop EPS, and there is no evidence to withhold PD therapy as a treatment option. There also is no evidence supporting a single rule about optimal length of PD treatment (ie, a recommended time that a patient can receive PD therapy without increasing the risk for EPS). Each patient should be considered individually, and the risk for EPS, as well as potential therapeutic interventions, should be openly discussed. Because dextrose exposure is a risk factor for EPS, it is essential to try to limit dextrose exposure from the beginning of PD treatment.

Future Directions

In addition to using glucose-sparing strategies, identifying individuals at increased risk for EPS may help with early diagnosis and therapy. One recent study suggested that early detection of and subsequent therapeutic intervention for EPS-prone patients might prevent the development of the condition. Effluent metabolic profiles and biomarkers are an active field of research. Longer term studies of the effects of biocompatible PD fluids on peritoneal membrane function may also be enlightening, especially considering results of the balANZ trial, in which transport status remained stable for 24 months in patients treated with biocompatible solutions, but increased in controls, who received standard PD fluid. There is also interest in early therapeutic interventions that may affect structural and functional changes in the peritoneal membrane that occur over time and may set the stage for the development of EPS. For example, use of ACE inhibitors or ARBs appears to help preserve the peritoneal membrane. Because the development of EPS is a complex process and likely multifactorial, a multipronged approach should be considered. Hopefully, results from these newer studies and future research will decrease the incidence and severity of EPS.

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NEW FRONTIERS

Urgent-Start PD

It has been demonstrated that starting HD therapy with a CVC is associated with decreased survival and increased infectious complications compared to initiation with a mature vascular access or PD catheter. Despite this, most patients in the United States initiate HD therapy with a CVC. Over the last few years, a growing body of literature has revealed that in the appropriate patients, urgent-start PD, or starting dialysis therapy within 2 weeks of PD catheter insertion, is a safe and effective alternative to starting dialysis with a CVC. This option of using PD catheters shortly after insertion has been the result of improved catheter placement techniques and low-volume protocols. Late referrals, patients who have not selected a renal replacement therapy modality, and those with unexpected worsening kidney function with no contraindication for PD can be considered for this therapy.

Urgent-start PD therapy can be initiated in the hospital or the outpatient setting. The initial prescription involves low-volume PD in the supine position to minimize the increase in intra-abdominal pressure and the risk for leaking. PD fill volumes are then increased incrementally over the next 2 weeks while patient training is initiated. The infrastructure requirements for an outpatient urgent-start PD program have been well outlined and include patient education and selection, urgent PD catheter

placement, nursing support, administrative support, and protocol-driven orders.

Reported outcomes from several groups have been excellent. The largest of these studies revealed that urgent-start PD therapy is associated with superior short-term survival, fewer hospitalizations, and lower infection rates compared to those starting HD therapy with a CVC. There also may be a cost benefit in the first 90 days. With regard to survival and peritonitis rates, outcomes are comparable to traditionally planned PD, but in one study, urgent-start PD was associated with higher hospitalization rates. There may be some increased risk for mechanical PD catheter complications (primarily leaks), and studies have yielded inconsistent results regarding technique survival. Even so, in the urgent setting, there are now quality data to support "PD First" in the appropriate patient.

PD for Acute Kidney Injury

Historically, PD therapy was successfully used for the treatment of acute kidney injury (AKI). However, in the 1990s, extracorporeal blood therapies became the standard of AKI care. In the last several years, there has been renewed interest in the use of PD for AKI. Potential advantages of PD over extracorporeal blood therapies include its technical simplicity, avoidance of the need for vascular access, gradual removal of solute, and the potential for earlier recovery of kidney function. Complications associated with PD for AKI include the risk for peritonitis and mechanical complications, including leakage and catheter dysfunction. There also are potential concerns regarding inadequate solute clearance, protein losses, and the effect of fluid in the peritoneal cavity on respiratory performance in ventilated patients. However, current studies have not demonstrated a significant negative effect due to these factors.

Data from Brazil have demonstrated that in critically ill patients with AKI, high-volume PD using automated cyclers can achieve outcomes comparable to those of daily HD. A recent systematic review found no significant differences in mortality between PD and extracorporeal blood therapies, but the overall methodologic quality of the included studies was thought to be low and most were conducted in low-resource regions. PD use in AKI continues to be widespread in low-resource areas and is expected to increase as a result of the Saving Young Lives project, which provides training and educational support in establishing hospital centers for treatment of patients with dialysis-requiring AKI. Based on the available evidence for using PD therapy for AKI, the ISPD recently published a set of guidelines to help standardize this practice. It would be interesting to consider the use of PD for AKI in the United States given the availability of cyclers and the opportunity to collect high-quality data on the use of PD catheters soon after placement.

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