

## CORE CURRICULUM IN NEPHROLOGY

### Peritoneal Dialysis

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**A**T THE END OF the millennium, there were 275,053 dialysis patients in the United States. Of these, 5.2% were on continuous ambulatory peritoneal dialysis (CAPD) and 4% on automated peritoneal dialysis (APD). The number of incident peritoneal dialysis (PD) patients using automated forms of PD, now estimated to be over 40%, has been increasing. In contrast to the experience in the United States, the number of prevalent end-stage renal disease patients on PD in other countries reaches as high as 60%. Reasons for differences are multifactorial and include, but are not limited to, access to PD, physician comfort/expertise with therapy, and government reimbursement policies.

#### COMPONENTS OF THE PERITONEAL DIALYSIS SYSTEM

Renal replacement therapy with PD requires 3 key components: (1) the PD catheter, (2) PD solutions, and (3) the peritoneal membrane and its associated vascular supply.

#### Catheter Issues

- *Acute Use Catheters:*
- Straight, relatively rigid conduits about 3 mm in diameter and 25 to 30 mm in length designed for short-term (2 to 3 days) use
- Can be placed at the bedside
- Significant risk of peritonitis, malfunction, and bowel perforation
- Seldom used

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- *Chronic Use Catheters:*  
Standard chronic indwelling PD catheters are made of soft materials, such as silicone rubber or polyurethane.
- Silicone rubber is used most frequently, relatively biocompatible, inert, no leachable plasticizers
- Polyurethane catheters: better wall strength, however, cracking of the catheter has been reported after use of topical polyethylene glycol, alcohol, or mupirocin
- *Design Modifications:*
- Straight PD catheters were associated with a high rate of external cuff extrusion and catheter migration
- “Swan-neck” catheter: lateral or downward external exit and a permanent bend in the subcutaneous portion
- Most catheters exit at the lateral abdominal wall, however, one modification uses a pre-external exit site (thought to be subject to less trauma and allows patients to “immerse” in water)
- *Catheter Implantation Techniques:*  
Implantation technique significantly influences long-term patient outcome.
- Sterile conditions are essential
- Experienced catheter insertion team
- A panel of experts has agreed on 5 general standards for catheter placement:
  - (1) the deep cuff should be in the anterior abdominal musculature;
  - (2) the subcutaneous cuff should be near the skin surface and not less than 2 cm from the exit site;
  - (3) the catheter exit should be positioned laterally;
  - (4) the exit site should be directed downward or laterally; and
  - (5) the intra-abdominal portion should be placed between the visceral and parietal peritoneum.
- *Surgical insertion* of catheters—most commonly used placement procedure in clinical practice today

- *Peritoneoscopic insertion*: allows direct visualization of the course of the catheter
- *Blind placement*: does not allow direct visualization of the catheter or peritoneum
- should not be used in markedly obese patients
- should be used in those who have had previous abdominal surgery
- *Moncrief-Popovich technique*: incorporates 2 modifications of conventional implantation procedures
- At time of implantation, the entire extraperitoneal portion of the catheter is placed subcutaneously
- At a subsequent date (4 to 6 weeks after implantation), the external portion of the catheter is exteriorized, so that dialysis can be initiated immediately
- *Catheter Break-In*: Normal to flush the peritoneal cavity with between 500 and 1,500 mL of dialysis fluid until clear immediately postplacement
- Heparin (500 to 1,000 U/L) can be added in cases where fibrin is present
- Optimally, PD should not be initiated until 10 to 14 days after catheter placement
- If PD must be started immediately postimplantation or before optimal catheter break-in, use intermittent dialysis with low dialysate volumes (ie, <1,500 mL) in the supine position
- *Catheter Survival*: Transfer from PD to hemodialysis due to catheter-related problems in about 20% of cases
- Often due to a catheter infection-related issue
- Occasionally due to catheter migration and to dialysate leaks
- 3-year catheter survival rate of 80% should be expected, with a minimally acceptable rate of 80% at 1 year

### **Dialysis Solutions**

- *Electrolytes*
- *Sodium*: Sodium has been added to the dialysis in varying concentrations ranging from 120 to 140 mEq/L (mmol/L), most have a Na<sup>+</sup> concentration of 132 mEq/L (mmol/L). Some studies have focused on the use of lower dialysate Na<sup>+</sup> concentrations to facilitate salt and water loss to better control hypertension, using dialysate Na<sup>+</sup>

concentrations of 98 to 120 mEq/L (mmol/L). Preliminary studies show an increase in net Na<sup>+</sup> loss and better volume and blood pressure control.

- *Potassium*: Potassium is usually not added to chronic PD fluids. Patients tend to lose about 35 to 40 mEq/day in the dialysate while maintaining a serum K<sup>+</sup> concentration of approximately 4.0 mEq/L (mmol/L).
- *Magnesium*: Dialysis solutions with an Mg<sup>2+</sup> concentration of 0.5 mEq/L are now widely used.
- *Calcium*: Historical dialysate fluids contained Ca<sup>2+</sup> concentrations of 3.5 mEq/L. If calcium salts were used as a phosphate binder, hypercalcemia (in 35% to 56% of patients) and metastatic calcification were frequently noted. Because of these complications, dialysis fluids were developed with a lower, nearly physiologic Ca<sup>2+</sup> concentration (2.5 mEq/L). With these fluids, there is a risk of net Ca<sup>2+</sup> loss in some patients, resulting in negative Ca<sup>2+</sup> balance and an increase in parathyroid hormone levels.
- *Buffers*
- Most commercially available PD fluids contain a racemic mixture of both D- and L-lactate as the buffer. Solutions have been very functional with patients surviving on PD for up to 20 years.
- Lactate-containing fluids are “bioincompatible”—all normal cellular functions of resident peritoneal cells are impaired; clinical significance unknown.
- Bicarbonate-based buffer system would be preferable but has been associated with many problems including precipitation of Ca<sup>2+</sup> and Mg<sup>2+</sup> carbonates; caramelization of glucose at physiologic pH during sterilization.
- To avoid these problems, a 2-chamber bag in which the 2 solutions are combined at the time of use has been developed.
- *Osmotic Agents*

Several substances have been tried as osmotic agents. These include both low molecular weight (glucose, glycerol, sorbitol, amino acids, xylitol, and fructose) and high molecular weight (glucose polymer, gelatin, polycation, dextrans, and polypeptides) agents. At present, glucose remains the standard osmotic agent although amino

acids and polyglucose are available for clinical use in most countries.

- *Glucose.* Standard dialysis solutions contain glucose as the osmotic agent. Glucose has been shown to be safe, effective, readily metabolized, and inexpensive. However, glucose is not an “ideal” osmotic agent because of the following properties or effects: rapid absorption; the potential for metabolic derangements (such as hyperglycemia, hyperinsulinemia, hyperlipidemia, and obesity); the necessity for an acidic dialysis pH to prevent caramelization; and the potential nonenzymatic glycosylation of peritoneal tissue. Glucose solutions induce a crystalloid osmotic gradient to drive ultrafiltration.
- *Amino Acids.* There is an obligatory daily loss of protein and amino acids into the peritoneal effluent. Therefore, a potential advantage of amino acid-containing fluids would be that the absorbed osmotic agent would be a non-phosphorous-containing protein caloric source and that the amino acids absorbed would replace or exceed the obligatory amino acids lost in the effluent on a daily basis. However, studies documenting the long-term efficacy of amino acids as a nutritional supplement have been controversial. Complications include the development of metabolic acidosis and increased levels of serum urea nitrogen. The use of 1.1% amino acid solutions results in ultrafiltration and solute clearance rates similar to those using 1.5% dextrose solutions.
- *Polypeptides/Oligopeptides.* Polymers of glucose (icodextrin or polyglucose) can induce a colloid osmotic force to drive ultrafiltration. Whereas glucose induces transcapillary ultrafiltration across both small interendothelial and ultrasmall transcellular pores (via crystalloid forces), glucose polymers induce ultrafiltration across interendothelial pores and the relatively few large pores (via colloid osmotic forces). Ultrafiltration with glucose is rapid and occurs early in the dwell (due to large crystalloid osmotic gradient) and decreases with time as glucose is absorbed, whereas with polyglucose, ultrafiltration is constant but slow.

In contrast to glucose-containing solutions, where the glucose is absorbed via small interen-

dothelial cells by diffusion, polyglucose is slowly absorbed through lymphatics. Thus, it can maintain its colloid osmotic force over long dwells of up to 18 hours. Furthermore, the rate of absorption is not influenced by peritoneal transport type, as is the absorption rate of glucose by diffusion. The safety of icodextrin use has been established. Reported side effects include skin rash and sterile peritonitis. Indications for the use of polyglucose include the long dwell of CAPD (overnight); the daytime dwell of continuous cyclic PD (CCPD); patients with loss of ultrafiltration (high transporters, patients with loss of aquaporins); during episodes of peritonitis; and in patients with diabetes mellitus (to decrease glucose load).

- *Biocompatibility Issues.* In a typical PD patient, the peritoneal cavity is exposed to new dialysis fluids at least 4 times daily. These dialysis solutions exert biologically and chemically induced effects not only on the peritoneal membrane and mesothelial cell, but also on the resident leukocytes, macrophages, and fibroblasts. Peritoneal biopsies in patients on long-term PD have revealed ultrastructural changes (eg, glycosylation of capillary proteins) possibly induced in part by the dialysis solutions. Data suggest that di(2-ethylhexyl)phthalate (DEHP), the most commonly used plasticizer for polyvinylchloride, may have adverse effects on macrophage function. Furthermore, it has been shown that glucose degradation products produced during heat sterilization and storage of glucose containing solutions participate in the nonenzymatic cross-linking of proteins leading to the formation of advanced glycosylation end products (AGEs).

- *Conclusions.* Although commercially available dialysis solutions based on lactate and glucose have provided adequate treatment of end-stage renal disease for thousands of patients, they do alter mesothelial cell and peritoneal macrophage function. Furthermore, pathologic alterations of the peritoneal membrane that may be related to components of the PD solutions have been described. Newer solutions that address these needs have been developed and are in clinical use. However, the long-term outcomes/benefits of such solutions for the patient are not yet fully understood.

### ***Peritoneal Membrane***

- ***Anatomy***

The peritoneal membrane is the primary interface between the blood and the dialysate compartments. This membrane is composed of 2 principal parts: (1) the parietal peritoneum (about 10% of total), which covers the inner surface of the abdominal and pelvic walls including the diaphragm; and (2) the visceral peritoneum (about 90% of total), which covers the visceral organs including the intra-abdominal portion of the gastrointestinal tract, liver, and spleen, and forms the omentum and the visceral mesentery, where it reflects over and connects the loops of bowel. The total surface area of the peritoneal membrane (parietal and visceral) is thought to approximate the body surface area in most adults (ie, 1 to 2 m<sup>2</sup>). Children have a disproportionately larger peritoneal surface area than most adults. The peritoneal cavity usually contains about 100 mL of fluid or less; however, a normal-sized adult can usually tolerate 2 L or more without discomfort or compromise of pulmonary function. From the perspective of PD, important anatomic components of the peritoneal membrane include the mesothelial cells, an underlying basement membrane, the interstitium, the microcirculation, and the visceral lymphatics.

- ***Mesothelium.*** The mesothelium is a continuous monolayer of cells ultrastructurally similar to type II pneumocytes found in the pulmonary alveoli. These cells secrete surfactant-like lubrication for the peritoneum, are active in modulating host defense, and have been shown to produce cancer antigen (CA) 125. The CA125 appearance rates in the dialysate effluent may be used to estimate mesothelial cell mass and possibly the effect of changing to more “biocompatible” solutions on overall peritoneal membrane health.
- ***Basement Membrane.*** A homogenous basement membrane underlies the mesothelial cells, is between 25 and 40 nm thick, and is believed to be composed of type IV collagen, proteoglycans, and glycoproteins.
- ***Interstitium.*** The interstitium is the supporting structure of the peritoneum and is composed primarily of a mucopolysaccharide matrix. It contains bundles of collagen fi-

bers, blood vessels, the lymphatics, occasional macrophages, glycosaminoglycans, and fibroblasts. There are aqueous and lipophilic phases. The aqueous phase mediates transport of water, electrolytes, protein, nutrients, and hormones.

- ***Blood Vessels.*** Total splanchnic blood flow in normal adult humans at rest ranges from 1,000 to 2,400 mL/min. The blood supply to the visceral and parietal membranes arises from 2 sources: (1) the celiac and mesenteric arteries, with venous drainage via the portal vein; and (2) the circumflex, iliac, lumbar, intercostal, and epigastric arteries draining directly into the systemic circulation, bypassing the hepatic portal system. The number of perfused capillaries determines the so-called “effective peritoneal surface area,” ie, functional area for exchange between blood and dialysate. The capillary walls are believed to contain at least 2 distinct pore sizes, with the larger pores located primarily at the venular end and the smaller pores at the arteriolar end. Endothelial cells also appear to have intracellular pores or channels thought to be aquapores.
- ***Peritoneal Lymphatics.*** As in most body tissue, there is a network of lymphatic vessels that aid in removal of fluids and solutes from the interstitium. The fluid absorption occurs primarily through stomata in the subdiaphragmatic area. Many physiologic factors notably alter the rate of lymphatic uptake, and these include intraperitoneal hydrostatic pressure, body posture, and pharmacologic agents.

### ANATOMIC FINDINGS IN PD PATIENTS

Clinical observations by surgeons experienced with CAPD patients suggest that the peritoneal surface develops a diffuse opacification at times with local accentuation, which can progress to the “tanned” peritoneal syndrome or, in advanced stages, to sclerosing encapsulating peritoneal fibrosis. In most patients, these changes are minimal, even in those who have been on PD for up to 10 years. The hypothesis is that chronic uremia is associated with high levels of circulating reactive carbonyl compounds (RCCs), which initiate AGE formation in the peritoneum. During PD, RCCs contained in glucose-containing

solutions (as a result of the sterilization process) will amplify AGE formation. The RCCs and AGEs initiate a number of cellular responses including vascular endothelial growth factor, which interacts with endothelial cells stimulating angiogenesis and increasing vascular permeability. Use of more biocompatible solutions may slow or prevent this process.

#### PERITONEUM AS A DIALYSIS SYSTEM

- *Resistance to Salt and Water Transport.* The barrier for mass transport appears to offer very little resistance to solute transport by diffusion but seems to offer significant resistance to solute transport by convection. The clinical significance of this is that solute removed by convection is not removed at the same concentration as it is in plasma. There is more resistance to flow for these solutes than there is for water. This is especially true when ultrafiltration is driven by small osmotic solutes, “crystalloid osmosis,” but it is less significant when ultrafiltration is driven by hydraulic pressure or colloid osmosis. An example of this is sodium “sieving” and the observation that, early in the dwell with a glucose-containing solution, dialysate sodium decreases.

The interstitium represents the longest distance that solutes must traverse. There is increasing evidence to suggest that the interstitium is one of the major resistance sites for urea and low molecular weight solute transport. The interstitium is thought to be represented by a 2-phase system that contains a gelatinous mucopolysaccharide matrix interspersed with a water-rich, colloid-poor, free-fluid phase containing aqueous channels.

- *Models of Peritoneal Transport*

Despite the complexity, investigators have attempted to characterize peritoneal membrane transport properties in terms of classical membrane physiology using mathematic models. These models can help the nephrologist understand peritoneal solute and water transport and guide in individualizing prescriptions for patients.

- “Distributed” models of peritoneal transport assume that the barrier separating blood from dialysate is not homogeneous but is composed of distinct elements, including

the capillaries and the interstitium, and that the blood phase is distributed within the peritoneal interstitium. This model includes the theory that the distance between capillary and mesothelial surface, as well as number of capillaries, influence transport.

- “Three-pore” model, yields the most realistic estimations of small-solute reflection coefficients, macromolecule transfer, and the effects of lymphatic absorption and ultrafiltration profiles observed clinically even when high-molecular-weight solutes are used as osmotic agents.

#### PHYSIOLOGY OF PERITONEAL TRANSPORT

- *Solute Transport by Diffusion*
- Diffusion, defined as a tendency for solutes to disperse themselves within the space available, is the most important mechanism responsible for solute transport into the peritoneum. In PD, the diffusive clearance of any solute depends on the “effective” peritoneal membrane surface area, the intrinsic permeability of the membrane, dialysate flow, concentration gradients, and time allowed for transport. Overall solute clearance can never exceed the lowest of these parameters. Typical dialysate flow rates are markedly lower than those of capillary blood flow or membrane transport capabilities. Standard PD therapies are therefore limited by dialysate flow.

Diffusion becomes more restricted as molecular weight increases (ie, urea diffuses faster than creatinine). In fact, in contrast to what is observed for small solute clearance where increasing number of exchanges per day tends to increase daily clearance even if already during 24 hours of dwell, once on 24 hours/day of dwell time, further increases in the number of exchanges/day does not increase middle molecule clearances.

- *Ultrafiltration:* Net ultrafiltration is achieved clinically by creating an osmotic pressure gradient (crystalloid or colloid) between blood and dialysate. Historically, dialysis fluids achieved this via crystalloid osmosis by adding various concentrations of glucose to the solutions. Newer fluids use polyglucose to induce colloid-driven ultrafiltration. Solutes present in body fluids can be swept

along with the bulk solvent flow even in the absence of a concentration difference for net diffusion, contributing to overall solute clearance. This contribution to net solute clearance has been termed “solvent drag” or “convection.”

- *Kinetics of Peritoneal Ultrafiltration:* In addition to ultrafiltration, absorption of fluid from the peritoneal cavity also occurs. This is mainly due to absorption of fluid through the tissues of the anterior abdominal wall and by the peritoneal lymphatics. Intraperitoneal volume at any time is therefore determined by the relative magnitudes of transcapillary ultrafiltration and anterior wall plus lymphatic absorption.

Polymers of glucose (icodextrin or polyglucose) can induce a colloid osmotic force to drive ultrafiltration. Whereas glucose induces transcapillary ultrafiltration across both small interendothelial and ultrasmall transcellular pores/aquaporins (via crystalloid forces), glucose polymers only induce ultrafiltration across interendothelial pores (via colloid osmotic forces). Ultrafiltration with glucose is rapid and occurs early in the dwell (due to large crystalloid osmotic gradient) and decreases with time as glucose is absorbed, whereas with polyglucose, ultrafiltration is constant but slow.

Thus, for 2-L solutions containing 1.5% dextrose (1.36% glucose), osmotic equilibrium and maximal drain volume are reached after about 2 hours of dwell time in most patients, whereas peak intraperitoneal volumes are not likely to occur until after a 3- or 4-hour dwell with 4.25% dextrose (3.86% glucose).

- *Solute Transport by Convection:* Solutes present in body fluids can be swept along with the bulk flow of water during ultrafiltration even in the absence of a concentration gradient for net diffusion. This solvent drag or “convective solute” transport does not occur in amounts per liter of ultrafiltrate equal to the physiologic concentration of solutes in body fluids. In other words, there is a sieving effect that depends on resistance forces intrinsic to the membrane and sol-

vents. This is most commonly observed during dwells with solutions containing glucose as the osmotic agent and is mainly due to water movement across transcellular aquaporins. The most important clinical consequences are those related to the transport of  $\text{Na}^+$ . These expected changes in dialysate  $\text{Na}^+$  concentrations during the dwell can be helpful in evaluating a patient with loss of ultrafiltration. If a patient is on automated therapy and there is aggressive overnight ultrafiltration, there may be relatively more water than sodium removal.

- *Lymphatic Absorption:* Intraperitoneal fluid is continuously absorbed from the peritoneal cavity. The fluid can either be absorbed directly into the subdiaphragmatic peritoneal lymphatics or through the interstitial tissue of the peritoneal membrane. Hydraulic pressure effects when standing or when associated with activity may alter the relative amount of convective movement of fluids and solute into the subdiaphragmatic or other lymphatics. Data suggest that increases in intraperitoneal pressure are associated with an increase in lymphatic absorption rates. Measurements of lymphatic absorption rates in CAPD patients using intraperitoneal dextran as a marker ranged from 0.1 to 3.5 mL/min with a median value of 1.0 ml/min or about 2.2 L/day.

#### CLINICAL OBSERVATIONS OF PERITONEAL MEMBRANE FUNCTION

*Characterization of Peritoneal Membrane Transport:* In the presence of infinite peritoneal capillary blood and dialysate flows, solute clearance is directly proportional to peritoneal surface area and indirectly proportional to overall resistance. A measurement of clearance under these conditions is a measurement of the intrinsic transport properties of the peritoneal membrane. Ideally, these measurements are primarily a function of peritoneal diffusive permeability (cm/min) and effective surface membrane area (in  $\text{cm}^2$ ). Measurements of mass transfer area coefficients (MTACs) are thought to approximate this state. However, as MTAC measurements are relatively complex, the simpler peritoneal equilibration test (PET) has become the standard tool

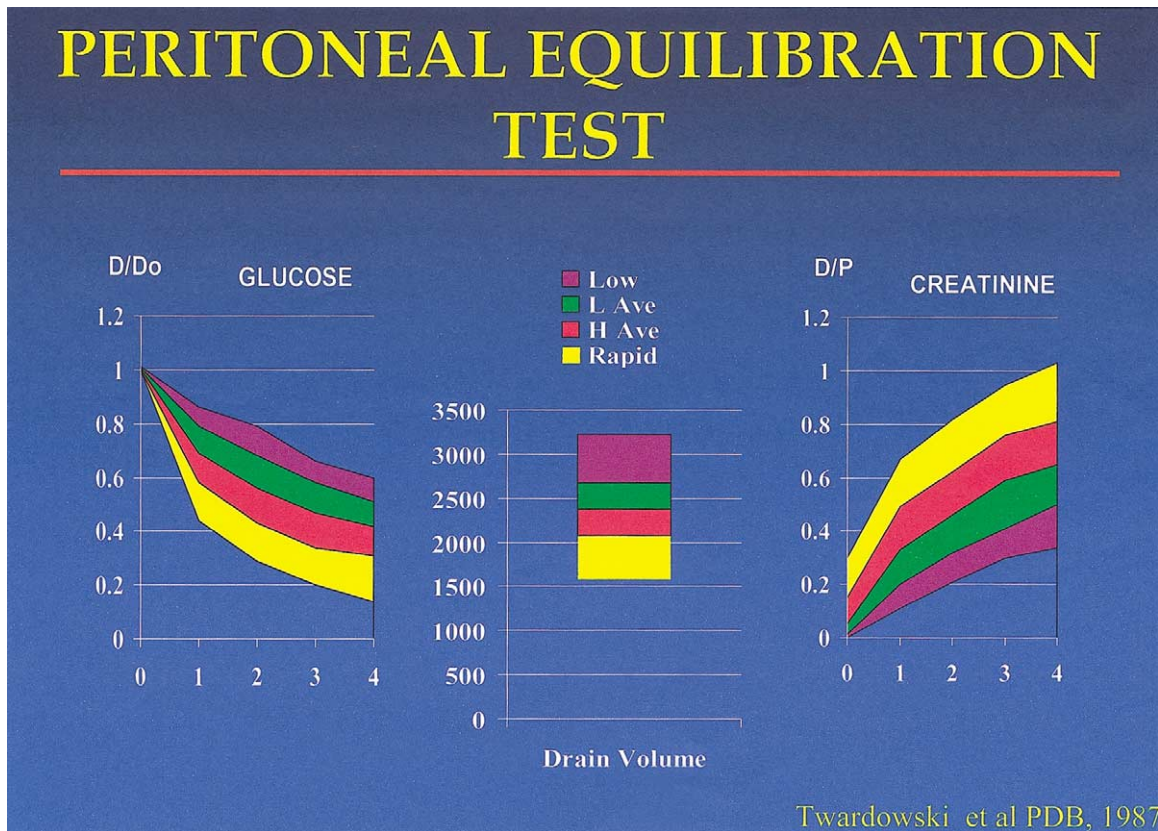


Fig 1. Peritoneal equilibration test. Reprinted with permission.<sup>20</sup>

used clinically to characterize peritoneal membrane transport. The protocol for the standard PET is as follows:

1. The test is performed in the morning after complete drain of the prior long ( $\geq 8$  hours) dwell.
2. Using 2.5% dextrose dialysate, the patient's usual fill volume is infused.
3. A sample of dialysate for determination of creatinine, urea, and glucose is taken immediately after infusion and at 2 and 4 hours.
4. A blood sample for determination of creatinine, urea, and glucose is taken 2 hours after infusion.
5. The dialysate is drained after 4 hours, and the drain volume is recorded.
6. The dialysate to plasma (D/P) ratios for creatinine and urea and the ratio of glucose in the dialysate compared to its initial concentration (D/D<sub>0</sub>) at times 2 and 4 hours are calculated and plotted on the standard PET graph (Fig 1).

As seen in Fig 1, peritoneal membrane transport is divided into 4 categories: high, high average, low average, and low. Patients who exhibit high membrane transport (lightest quartile) will most rapidly equilibrate creatinine (and urea) and achieve excellent solute clearance. However, they also rapidly absorb glucose from the peritoneal cavity, thereby dissipating the osmotic gradient favoring ultrafiltration. Therefore, they have low drain volumes and will often, in fact, reabsorb fluid from the peritoneal cavity during long dwells. These patients will often benefit from performing CCPD with more frequent exchanges and shorter dwell times. They may also benefit from the use of icodextrin during their long day dwell. Conversely, patients who exhibit slow membrane transport (darkest quartile) have poorer solute clearance. Therefore, these patients may benefit from longer dwell times (CAPD) and larger exchange volumes. However, because they dissipate their osmotic gradient slowly as well, these patients

ultrafilter very well. Patients in the 2 average groups tend to do well with both solute clearance and ultrafiltration.

*Stability of Peritoneal Membrane Over Time:* Longitudinal observations in CAPD patients suggest that most patients have no significant change in small solute clearance over time. If anything, there tends to be an increase in vascularity resulting in an increase in the D/P ratio of small solutes. It should be noted, however, that D/P ratios are influenced by instilled volume, rate of diffusion, net ultrafiltration, and solute transport by convection. Therefore, a change in a D/P value does not necessarily indicate that the patient's MTAC, ie, intrinsic membrane permeability, has actually changed.

#### CHOICE OF DIALYSIS MODALITY

Potential indications of PD include patients who have problematic vascular access, or who prefer home dialysis but cannot perform home hemodialysis due to a lack of a partner or suitable home environment. Absolute contraindications to PD include a documented loss of peritoneal function or extensive abdominal adhesions that limit dialysate flow. Under these conditions, it will not be possible to achieve an adequate dose of dialysis.

There are a number of relative contraindications to PD. Body size limitations are probably the most common cause. When anuric, it is difficult, but not impossible, to achieve current Kidney Disease Outcomes Quality Initiative (K/DOQI) targets for adequate dialysis in patients who weigh more than 100 kg. Other relative contraindications include patients with bowel pathology, specifically diverticulitis, ischemic bowel disease, or inflammatory bowel disease; abdominal wall or skin infections increase the risk of catheter exit-site infection and thus increase the risk for peritonitis. Although, there are reports of doing PD in some patients who have either an ileostomy or a colostomy, an abdominal prosthesis should be in place for a minimum of 6 weeks, and sometimes as long as 16 weeks, to allow sufficient time for complete healing prior to initiating PD. Although the presence an abdominal aortic prosthetic graft is not a contraindication to PD, there is limited clinical experience in this area.

#### ● *Peritoneal Dialysis Modalities*

- *CAPD.* Typically patients perform 4 manual exchanges/day. A newer modification of CAPD incorporates 1 nighttime exchange with a simple nightly exchange device; that is, the patient receives a total of 5 exchanges/day, with 2 overnight exchanges and 3 exchanges during the day.
- *Cycler Dialysis.* Patients on CCPD will typically program the cycler to perform multiple automated exchanges overnight. Most then perform a last bag fill; that is, the machine will deliver a dialysate exchange at the end of the nighttime cycler dialysis.

A minority of patients will perform cycler dialysis overnight and not perform a last bag fill. Thus, these patients have a dry day; they do not carry any dialysate in their peritoneal cavity during the day.

- *Tidal Peritoneal Dialysis (TPD).* TPD consists of the repeated instillation of small tidal volumes of dialysis fluids with the use of an automated cycler. There is little evidence to suggest that TPD can provide clearances that are superior to that provided by cycler dialysis.

#### ADEQUACY OF PERITONEAL DIALYSIS

The National Kidney Foundation (NKF)/DOQI clinical practice guidelines, first published in 1997 and subsequently revised in 2000, provide evidence-based guidelines for the provision of adequate PD. These guidelines provide recommendations about when to initiate dialysis, how and when to measure PD dose, and recommendations for an adequate dose of dialysis.

- *Measurement of Peritoneal Dialysis Dose:* Solute clearance occurs by both residual renal and peritoneal removal of solutes. Thus, when measuring total solute clearance, both volumes should be collected. One currently uses weekly  $Kt/V_{\text{urea}}$  and total weekly creatinine clearance normalized to 1.73 m<sup>2</sup> body surface area (BSA). This testing should be done more frequently if there has been either a significant change in clinical status or if there has been a change in the PD prescription. One could target PD dose by ignoring the residual renal component in their calculations, rely-

ing on peritoneal clearance alone if indicated. If residual renal clearances are included, the calculations for  $Kt/V_{\text{urea}}$  are obtained using urea clearance, while one uses an estimation of glomerular filtration rate (the mean of the urea and creatinine clearances) for the weekly creatinine clearance measure.

- *Adequate Dose of Peritoneal Dialysis:* Based on the results of many clinical studies performed during the past 10 years, the NKF/DOQI workgroup has developed guidelines for an adequate dose of dialysis. For CAPD patients, the delivered PD dose for  $Kt/V_{\text{urea}}$  should be at least 2.0. The recommended weekly creatinine clearance dose is based on the patient's transport characteristics. For patients who are high or high average transporters, the total creatinine clearance should be at least 60 L/wk/1.73 m<sup>2</sup>. For patients who are low or low average transporters, the weekly creatinine clearance should be at least 50 L/wk/1.73 m<sup>2</sup>. The dosage recommendations for automated techniques are based on whether the patient also has daytime exchanges. For patients using the cycler who have a dry day, the total  $Kt/V_{\text{urea}}$  should be at least 2.2 and the weekly total creatinine clearance should be at least 66 L/wk/1.73 m<sup>2</sup>. For patients using the cycler who have at least 1 daytime dwell, the total  $Kt/V_{\text{urea}}$  should be at least 2.1 and the total weekly creatinine clearance should be at least 63 L/wk/1.73 m<sup>2</sup>. In malnourished patients, the estimate of body size is adjusted up to ideal body weight. Thus, for  $Kt/V_{\text{urea}}$ , the target dose is increased by the ratio  $V_{\text{desired}}/V_{\text{actual}}$ , while for creatinine clearance the target dose is increased by the ratio  $BSA_{\text{desired}}/BSA_{\text{actual}}$ .

After the last PD guidelines were revised by the NKF/DOQI workgroup, the ADEquacy of PD in MEXico (ADEMEX) trial was published. A total of 965 subjects were randomized to either standard care, where patients continued on their present PD prescriptions, or to an interventional group, in which the dialysis prescriptions were modified to achieve a peritoneal creatinine clearance of 60 L/wk/1.73 m<sup>2</sup>. The mean separation in peritoneal creatinine clearances in the 2 groups was approximately 10 L/wk/1.73 m<sup>2</sup>. Residual

renal function was similar in the 2 groups. Patient survival was similar in the interventional and standard groups, even after adjustment for comorbid conditions such as age, presence of diabetes mellitus, serum albumin levels, anuria, and normalized protein equivalent of total nitrogen appearance. As a result, guidelines for adequacy of PD are likely to be revised.

#### WRITING THE DIALYSIS PRESCRIPTION

- *Initial Prescription:* The PD prescription can be developed either empirically or through the use of a computer-modeling program using data based on the patient's weight, residual renal function, and any lifestyle constraints that may be present.
- *Adjustments to the Initial Dialysis Prescription:* Two to 4 weeks following the initiation of PD, 24-hour collections of urine and dialysate should be performed, along with serum chemistries and a complete blood count, in order to calculate the weekly  $Kt/V_{\text{urea}}$  and creatinine clearance. The initial PET should be performed approximately 1 month after the initiation of dialysis. This waiting period is recommended as the PET results can change during the first month of dialysis. The PET is performed to rule out unexpected problems and also to identify patients who are either high or low transporters. High transporters will likely need short dwell prescriptions and may develop ultrafiltration problems as residual kidney function fails. Low transporters usually require high dose CAPD or CCPD in order to maintain adequate dialysis as residual renal function decreases. If clearances are at or above target, then monitor adequacy at regular intervals as noted in the section measurement of PD dose above. If clearances are below target, then modify the prescription and repeat adequacy testing.
- *Further Adjustments to the Dialysis Prescription:* For CAPD patients, there are 2 methods that can be used to increase dialysis adequacy. The most common approach is to increase the dwell volume/exchange. One could also increase the number of exchanges/day. Alternatively, a nocturnal exchange device is available that provides an extra exchange overnight, thus provid-

ing the patient with a total of 5 exchanges per day. For cyclor patients, there are several methods available for improving adequacy. These methods include increasing the dwell volume/exchange, increasing the time spent overnight on the cyclor, increasing the number of exchanges on the cyclor, or increasing the number of daytime dwells. Sometimes a combination of the above measures is used in an individual patient.

#### COMPLICATIONS OF PERITONEAL DIALYSIS

Patients performing PD may experience either infectious or noninfectious complications.

##### ● *Infectious Complications*

Infectious complications account for approximately two thirds of all PD catheter losses and around one third of all transfers to hemodialysis. The major infectious complications of PD are peritonitis and exit-site or tunnel infections.

##### ● *Peritonitis*

The most common infectious complication of PD.

- A significant cause of hospitalization, catheter loss, malnutrition, peritoneal membrane failure, and occasionally death.
- Average frequency approximately 1 episode per 20 to 30 patient-months. The use of disconnect systems has played a major role in lowering this frequency from the prior rate of 1 episode per 6 to 18 patient-months.
- Diagnosed when at least 2 of the following are present:

Cloudy dialysis effluent with white blood cell count  $>100$  cells/mm<sup>3</sup> (usually  $>50\%$  are polymorphonuclear neutrophils)—present in 98% of cases

Abdominal pain—present in approximately 75% of cases

Positive culture from dialysate

Other symptoms such as fever, nausea, or diarrhea are present in no more than half of all cases.

Not all instances of cloudy peritoneal dialysate reflect infectious peritonitis. Depending on the cellularity of the fluid and the nature of the cells found, other causes such as fibrin, triglycer-

ides, juxtaperitoneal infection, malignancy, or allergic reactions should be considered.

##### ● *Microbiology*

Sixty to seventy percent of episodes are due to Gram-positive cocci, most commonly *Staphylococcus aureus* or *epidermidis*. Gram-negative rods account for 15% to 25% and fungi for 2% to 3%. In approximately 15% of episodes, no organism is cultured. Tuberculosis is a rare cause of peritonitis in the United States.

The finding of anaerobic and/or polymicrobial peritonitis should raise the question of an intraabdominal catastrophe and prompt a surgical evaluation. When due to pancreatitis or a ruptured viscus, peritonitis may be associated with an elevated amylase ( $>50$  IU/L) in the dialysate.

##### ● *Treatment*

Send dialysate for cell count with differential and Gram stain. Initiate therapy guided by Gram stain results.

The International Society for Peritoneal Dialysis (ISPD) recommendations for the initial/empiric therapy of peritonitis have changed over the years. The current recommendations are:

Gram Stain Results	Therapy
Gram-positive	First-generation cephalosporin
Gram-negative	Third-generation cephalosporin (an aminoglycoside may be used for patients with residual urine output $<100$ cc/d)
No organism seen	Combination of above agents

The use of vancomycin remains controversial. The ISPD no longer recommends routine use of vancomycin for fear of inducing vancomycin resistance in *enterococci*. However, other authors still prefer it because of the high frequency of methicillin-resistant, coagulase-negative *staphylococci*.

Attempts at treating fungal peritonitis with amphotericin or a combination of fluconazole and flucytosine virtually always fail. Catheter removal should be considered very early.

Final therapy should be guided by culture results and sensitivities. Treatment should be continued for a total course of 2 weeks; infections due to *S aureus*, anaerobes, members of the *Pseudomonas/Stenotrophomonas* family, or those due to multiple Gram-negative organisms require 3 weeks of antibiotic therapy.

- *Relapsing Peritonitis:*

Recurrence of peritonitis with the same organism within 4 weeks of the completion of therapy signifies relapse.

The recommended treatment for relapsing peritonitis is:

Organism	Therapy
Gram-positive	First-generation cephalosporin + rifampin for 4 wk (use vancomycin or clindamycin in case of methicillin-resistance, ampicillin and an aminoglycoside for enterococcus)
Gram-negative <i>Pseudomonas/</i> <i>Stenotrophomonas</i>	Remove catheter
Other	Third-generation cephalosporin (an aminoglycoside may be used for patients with residual urine output <100 cc/d)

Relapsing peritonitis due to *S aureus* should prompt consideration of an occult tunnel infection (*Vida infra*).

Relapsing peritonitis due to Gram-negative organisms (or Gram-positives that fail to respond after 96 hours of therapy) should prompt consideration of an intra-abdominal abscess. Ultrasonography or computed tomographic scanning of the abdomen with intraperitoneal contrast may be useful in establishing the diagnosis. Strong consideration should be given to surgical exploration and catheter removal.

Another potential concern when faced with relapsing peritonitis, especially when due to coagulase-negative *staphylococci*, is the presence of bacterial biofilm (so-called "slime") on the catheter. Intraperitoneal instillation of thrombolytic agents will sometimes prove successful in eradicating the infection.

When catheter removal is necessary, it is generally wise to wait 3 weeks or longer before placing a new catheter as removal of the foreign body is often beneficial in promoting resolution of infection. However, it is sometimes possible to place the new catheter simultaneously provided the white blood cell count of the dialysate has decreased to <100/mm<sup>3</sup>. This should not be done for relapsing peritonitis due to known or suspected intra-abdominal abscess or when the

offending organism is a member of the *Pseudomonas/Stenotrophomonas* family, fungus, or mycobacterium.

- *Exit-Site Infection*

- Defined by the presence of purulent drainage with or without cutaneous erythema at the catheter-epidermal interface.
- Incidence ranges from 0.05 to 1.0 per patient-year.
- Results in peritonitis in 25% to 50% of cases and contributes significantly to catheter loss.
- Trauma to the exit-site, an upward-directed exit-site, or proximity of the distal catheter cuff to the exit-site (<2 cm) all predispose to exit-site infection.
- The bacteriology of exit-site infections is very similar to that of peritonitis.
- Treatment:

Send exit-site drainage for culture and Gram stain.

Current recommendations for initial/ empiric therapy:

Gram Stain Results	Therapy
Gram-positive	First-generation cephalosporin, trimethoprim/sulfamethoxazole, or penicillinase-resistant penicillin
Gram-negative	Oral quinolone
No organism seen	Gram-positive coverage only

It may be necessary to add rifampin for recalcitrant Gram-positive infections or a second Gram-negative agent for infections with *Pseudomonas*.

Topical antibiotic therapy is not recommended. However, the frequency of routine exit-site care should be increased to twice daily. Application of dressings soaked in 3% saline or povidone-iodine solution may be beneficial.

Prolonged treatment (4 to 6 weeks) may be necessary. Failure to eradicate the infection by that time should prompt consideration of catheter removal. Simultaneous catheter replacement at a remote site is usually successful with the exception of infections due to *Candida* or *Pseudomonas*.

The frequency of exit-site infections and peritonitis, particularly those episodes due to *S aureus*, is approximately 4- to 7-fold higher in

patients who are nasal carriers of *S aureus*. Prophylactic treatment of PD patients with oral rifampin or with mupirocin administered either intranasally or topically at the exit-site have all been shown to markedly reduce the frequency of both exit-site infections and peritonitis. Controversy remains as to whether all patients or only documented carriers should be treated in this fashion.

- **Tunnel Infection**

- Defined by the presence of erythema, edema, and/or tenderness over the subcutaneous catheter pathway associated with sanguinous, purulent, or thick drainage either spontaneously or when pressure is applied to the catheter tunnel.
- A loculated abscess involving the tunnel may present with pain or signs of inflammation without discharge. Ultrasonography of the tunnel may be helpful in establishing the diagnosis.
- Tunnel infections are commonly associated with simultaneous exit-site infection with the same organism; when this is the case the risk of peritonitis is increased.

Treatment of tunnel infections is very difficult. Antibiotic therapy is often unsuccessful. Irrigation of the tract with saline or a povidone-iodine solution is rarely beneficial. When due to Gram-positive organisms it may be possible to successfully treat the infection by deroofting a portion of the catheter tunnel; this technique is not successful for Gram-negative infections. Catheter removal and replacement is frequently necessary; this may sometimes be accomplished successfully in a single operation as described earlier in the section on peritonitis.

- **Noninfectious Complications**

As is the case for hemodialysis, patients performing PD are subject to numerous complications affecting many organ systems. This portion of the curriculum, however, will be confined to a discussion of complications specific to the performance of PD.

- **Catheter Malfunction**

- **Obstruction**

- PD catheters may exhibit obstruction during either the infusion or drain phases of an exchange.

- Failure of the PD catheter during infusion may reflect intraluminal obstruction by fibrin or clot. Flushing the catheter with heparinized saline may be beneficial. Thrombolytic therapy is often needed.
- Distended loops of bowel due to constipation will often impair catheter outflow by occluding many of the holes on the distal end of the PD catheter. This should always be considered as the first possible etiology for outflow obstruction and should be addressed with appropriate laxative therapy.
- Catheter obstruction may also be due to any of a variety of other causes including:

Adhesions due to prior peritonitis or surgery may cause the catheter to be trapped in a loculated compartment. Surgical lysis or catheter repositioning/replacement may be necessary.

Catheters with the distal tip in the abdomen rather than the pelvis may be subject to wrapping by active omentum (which does not commonly extend into the pelvis). In this circumstance inflow of dialysate is usually not affected, as the pressure of the infusing dialysate will displace the offending “flap” of omentum. Omental wrapping most commonly presents within the first few months of initiating PD and is generally painless. Omentectomy is often necessary.

Peritonitis, particularly that due to fungi, may present with catheter obstruction.

- **Malposition**

- Though occasionally due to inappropriate catheter placement at the time of insertion, malposition of the PD catheter is more commonly due to migration of the catheter tip out of the pelvic gutter into the upper abdomen. This is often associated with discomfort, localized by the patient to the site of the catheter. Malposition may also be a cause of poor catheter drainage, particularly in patients attempting to drain in the upright position. Changing position during drain (eg, lying on the right side for catheters in the right upper quadrant) may provide relief.
- Catheter tips that have migrated to the left upper quadrant may spontaneously reposition themselves secondary to the actions of peristalsis favoring downward movement of the catheter on the left side. In contrast,

spontaneous repositioning of a catheter that has migrated into the right upper quadrant is very unlikely as peristalsis favors continued upward movement of the catheter on this side.

- When catheter malfunction due to migration is present and spontaneous repositioning does not occur, mechanical intervention is necessary. The catheter position may be corrected by intraluminal manipulation with a stiff guide wire, use of a Fogarty catheter, or surgery (often laparoscopic). Some surgeons will suture the catheter to the dome of the bladder or internal abdominal wall to “tack it” into place.

- *Pain*

Patients performing PD may experience pain associated with either the inflow or drain phases of a PD exchange. Patients may also experience generalized pain bearing no direct temporal relationship with the performance of an exchange.

- *Pain on Inflow*

Commonly due to “jet” effect of dialysate emerging from the distal end of the catheter at relatively high velocity, thereby irritating the adjacent tissues. This is seen more frequently with straight catheters than in those with a curled tip.

Also caused by the relatively low pH (5.2) of the dialysate; exacerbated by increasingly hypertonic solutions.

May decrease with time on PD.

May diminish with the addition of lidocaine to solution bags prior to infusion.

Best treatment would be use of normal pH fluids; not currently available in the United States.

- *Pain on Outflow*

Unrelated to pH; rather, due to suction effect on intra-abdominal viscera.

Commonly localizes to the rectal or suprapubic areas.

Usually worse in APD than CAPD and often positional. Usually worse toward end of drain. May reflect poor catheter position.

May resolve with time. If it fails to resolve, pain may be lessened by incomplete drainage (eg, tidal dialysis). Catheter repositioning or removal may be necessary.

- *Generalized Pain*

Patients performing PD may occasionally experience pain in the lower back or shoulder.

- *Back Pain*

Back pain may be due to either alterations in posture induced by the presence of several liters of intraperitoneal fluid or due to the weight of the fluid itself. It may respond to exercise training. Alternatively, a change to APD with no or minimal daytime dwell volumes may be beneficial.

- *Shoulder Pain*

Shoulder pain may reflect irritation of the underside of the diaphragm due to the presence of either peritoneal dialysate or intraperitoneal free air.

May diminish when draining in Trendelenburg position.

Usually resolves without specific treatment.

- *Abdominal Fullness*

Many patients performing PD complain of a sense of abdominal “fullness.” This becomes problematic when patients feel too full to eat. This has long been thought to be simply a mechanical consequence of the presence of a large volume of intraperitoneal fluid. However, the magnitude of the symptoms have recently been demonstrated to be proportional to the caloric content of the dialysate as patients do not experience equally severe symptoms when carrying similar volumes of dialysate devoid of caloric content (eg, polyethylene glycol).

- *Membrane-Related Complications*

- *Ultrafiltration Failure*

Please see the section on “Physiology of Peritoneal Dialysis” for the diagnostic and therapeutic approaches to ultrafiltration failure.

- *Sclerosing Encapsulating Peritonitis (SEP)*

This is a rare but serious entity characterized by a thick-walled membranous “cocoon” encasing and entrapping loops of bowel. Patients present with abdominal pain, nausea, emesis, bowel obstruction (either small or large), and ultrafiltration failure with poor solute transport. The mortality rate is greater than

50% despite medical and surgical treatment. The etiology and pathogenesis of SEP are not well understood. SEP may present years after discontinuation of PD, even after renal transplantation.

- *Defects in Peritoneal Cavity Boundaries*
- *Hernias and Abdominal Wall or Genital Edema*

Due to the increase in intraabdominal pressure associated with the performance of PD, hernia is a relatively common complication occurring in anywhere from 10% to 25% of all PD patients. Hernias may be incisional (catheter site or other), ventral, umbilical, or inguinal. It has been suggested that the frequency of hernias may be increased in females.

Hernias often present with localized swelling that is usually painless. In these instances the diagnosis may be established via peritoneal scintigraphy or computed tomographic peritoneography. It should be noted, however, that intestinal obstruction due to strangulation may occur in up to 10% to 15% of hernias, particularly those at the catheter site or related to other abdominal incisions.

Dialysate leakage through congenital (eg, patent processus vaginalis) or acquired (eg, pericatheter or prior incisional site) abdominal wall defects results in dissection of dialysate through soft tissue and fascial planes. This will present with either genital (scrotal or labial) edema or generalized swelling of the abdominal wall and/or upper thigh, frequently with a *peau d'orange* appearance. Ultrasound or computed tomographic peritoneography are usually diagnostic. The latter may be performed without radiocontrast, as the presence of the dialysate itself may serve in this fashion and allow for definition of the defect.

While dialysate leaks may occasionally resolve after temporary cessation of PD or a switch to nocturnal intermittent PD, surgical repair is nearly always necessary. Abdominal hernias invariably require surgical repair.

- *Hydrothorax*

Hydrothorax is a rare complication (<2%) of PD. For unknown reasons there is a marked female preponderance. It most commonly be-

comes manifest within the first month of initiating PD; onset later than 1 year after the initiation of PD is uncommon. Peritoneal dialysate transits the diaphragm either via lymphatics or through congenital diaphragmatic defects. Nearly 90% of cases occur on the right side. The reason for this is unclear; protection of the left hemidiaphragm by the heart and pericardium has been postulated, as has a "piston" effect of the liver to propel dialysate across the right hemidiaphragm.

Patients most commonly present with progressive dyspnea and/or orthopnea. Pain and acute onset of dyspnea are uncommon.

*Diagnosis*—The pleural fluid is transudative and has a high glucose concentration. The cell count is variable. The diagnosis of PD-associated hydrothorax is confirmed by demonstrating communication between the peritoneal and pleural spaces. This may be accomplished by injecting radiolabeled albumin or technetium sulfur colloid into the peritoneal cavity and imaging the chest after allowing the patient to ambulate for an hour.

*Treatment*—Patients may require thoracentesis for initial relief of symptoms. PD should be temporarily discontinued or, at a minimum, changed to a modality associated with lower peak intraabdominal pressures, eg, lower volumes or nocturnal intermittent PD. Pleurodesis with talc, triamcinolone, autologous blood, tetracycline derivatives, fibrin glue, or *Nocardia rubra* cytoskeleton may be attempted in case of recurrence. The procedure is often poorly tolerated due to pleural irritation. Surgical repair via a limited thoracotomy is indicated if pleurodesis fails. Alternatively, patients may elect to transfer to hemodialysis.

- *Metabolic Abnormalities*

- *Hypoalbuminemia*

Patients performing PD lose approximately 4 to 7 g of albumin per day across the peritoneal membrane. Therefore, hypoalbuminemia is more commonly observed than in patients performing hemodialysis. Consequently, efforts should be made to maintain the patients' dietary protein intake  $\geq 1.2$  g/kg/d if at all possible.

- *Weight Gain, Hypertriglyceridemia, Hyperglycemia*

More than half of all PD patients will experience 1 or more of these problems that arise due to the increased caloric load provided by the dialysate. A low-fat diet, increased activity, and strict adherence to fluid restriction, thereby minimizing the need for hypertonic dialysate, will help attenuate these problems. Use of the non-glucose-based dialysate, icodextrin, as an alternative osmotic agent for the long dwell may be beneficial as well.

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