Complications of Peritoneal Dialysis

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Introduction

Patients with chronic disease have an increased risk over time to develop medical and/or surgical complications related to either the underlying disease or its treatment. These disease complications can have a significant impact on overall patient morbidity and survival. Currently an estimated 120,000 patients utilize peritoneal dialysis (PD) for the treatment of end-stage renal disease (ESRD) worldwide. Even though the actual percent of patients treated with PD differs by country (England 48%, US 14 %, Japan 6%, Australia 31%, France 10%), similar modality-specific complications may occur. Table 1 summarizes a wide range of modality-specific or organ-system complications that have been reported in patients on PD. Patient survival varies by complication rate, age, presence of diabetes mellitus (DM), and systemic competing risks; these characteristics vary by country and sociodemographic group. Peritonitis remains the major cause of drop out from PD programs. Infectious complications account for 43 – 50% of all patient admissions, 36.3% of hospital days, 22% of catheter complications, and 19.8% of technique-related complications. Various additional complications may be related directly or indirectly to the actual dialysis technique. Complications result in a higher rate of hospitalizations, greater length of stay and post hospitalization morbidity. Strategies to anticipate complications in the outpatient setting which significantly increase the risk for hospitalization should be developed.

Table 1. System Categories for Complications of Peritoneal Dialysis (events, clinical/laboratory findings) and Hospitalization Complications

1. Technique-specific/Non-infectious
- Membrane failure: true and apparent
- Sclerosing encapsulating peritonitis (SEP)
- Catheter-related: placement, hernia, malfunction, leak, perforation, other
- Hemoperitoneum
- Dialysis-related pain syndrome: inflow, outflow, generalized

2. Infections
- Peritonitis: typical organisms, atypical organisms, eosinophilic, sterile
- Catheter exit site (CESI): acute, chronic, tunnel, trauma
- *S. aureus* nasal carriage
- Antibiotic toxicity (gentamicin, vancomycin, quinolones)
- Vancomycin-resistent enteriococci (VRE)

Table 1. continued

3. Cardiac/Vascular
– Myocardial structural abnormalities (left ventricular hypertrophy, systolic dysfunction, infarction)
– Valvular abnormalities and calcification
– Arrhythmias
– Atherosclerosis: hyperlipidemia: cholesterol, triglyceride, Lp(a), homocysteinemia
– Abnormal vascular pro-ischemic factors
– Vascular calcification
– Vascular disease patterns: central, peripheral, cerebral
– Blood pressure: hypotension/hypertension
– Autonomic insufficiency
– Pericardial abnormalities: infection, inflammation

4. Musculoskeletal
– Hypocalcemia, hypercalcemia, hyperphosphatemia
– Low-turnover bone disease (adynamic bone disease)
– Dialysis-associated amyloid: B2 microglobulin amyloidosis, cervical spondoarthropathy
– Erosive azotemic arthropathy
– Osteopenia, abnormalities in mineral density/flouride
– Carpal tunnel syndrome
– Myopathy
– Extraskeletal calcification: periartcular, soft tissue
– Back pain
– Other: tendonitis, tendon rupture, capsular tear, inflammation, fluoride abnormality
– Oxalate abnormalities

5. Pulmonary
– Hydrothorax
– Respiratory function abnormalities
– Bronchopulmonary infections
– Metastatic pulmonary calcification
– Pulmonary edema
– Sleep-related respiratory disorders

6. Metabolic
– Acid-base abnormalities: lactic acidosis, metabolic acidosis
– Electrolyte/mineral disorders: hypokalemia, hypophosphatemia, hypomagnesemia, hyperkalemia, hypernatremia, hypermagnesemia, decreased sulfate
– Malnutrition: high-transport protein losses, amino acid abnormalities
– Uncontrolled diabetes mellitus / advanced glycosylation end products (AGE)
– Growth retardation
– Hormonal abnormalities
– Obesity

7. Neurologic / Psychiatric
– Cerebral metabolic abnormalities
– Psychological abnormalities: depression, noncompliance, cognitive dysfunction
– Multiple neuropathies: rapidly evolving polyneuropathy, ischemic optic atrophy, chronic inflammatory demyelinating polyneuropathy, diabetic/uremic neuropathy
– Restless legs, nocturnal myoclonus
– Autonomic neuropathy
– Cerebral vascular disease: multi-infarct, dementia, embolic stroke
– Altered quality of life: job-related stress, disrupted work function

Table 1. continued

8. Gastrointestinal
– Pancreatitis
– Motility abnormalities: gastroparesis, reflux, bloating
– Gastroesophageal reflux/bloating
– Nonobstructive mesenteric infarction (NOMI)
– Ascites: standard, chylous
– Gastrointestinal bleeding
– Hepatic complications: steatonecrosis, hepatitis C, hepatitis B, hepatitis G, liver abscess
– Esophagitis: infectious, inflammatory
– Ischemic/necrotizing colitis
– Esophageal rupture
– Drug toxicity: cisapride

9. Dermatologic / Other
– Pruritus
– Calciphylaxis
– Contact/hypersensitivity dermatitis
– Drug toxicity

10. Hematology / Oncology
– Anemia / red blood cell metabolism: infection/rHu-EPO response, angiotensin converting enzyme (ACE)
  inhibitors
– Abnormal platelet morphology and function
– Coagulation abnormalities: hypercoagulability, fibrinolysis
– Bleeding diuresis
– Neoplasia: renal cystic disease, urologic tumors, peritoneal

11. Transplant / Immune
– Graft rejection
– Post-transplant infection: pancreatitis, PD catheter
– Renal allograft thrombosis
– Post transplant ascites
– Immune defects: systemic, intraperitoneal
– Hypogammaglobulinemia
– Dialysate-induced immune defects
– Systemic lupus erythematosus (SLE) reactivation

12. Hospitalization risk/complication
– Increased hospitalization
– Modality mortality effect
– Special populations at risk: HIV, elderly, diabetic, high-transport patients
– Postoperative complications:
  – malnutrition (enteral feeding, gastrostomy, jejunostomy)
  – uncontrolled hyperglycemia
  – inadequate solute clearance
  – postoperative wound infection (amputation, revascularization, cardiac, aorto-femoral)
  – respiratory failure (re-intubation)

Technique-specific (Noninfectious) Complications

Peritoneal Membrane Failure

Long-term alterations in the peritoneal membrane are most likely related to the continuous exposure of the membrane to dialysate solutions containing glucose, low pH, and lactate. Little data are available on long-term PD membranes, resulting in discrepancies in the literature on membrane transport characteristic changes. A number of reports have suggested that creatinine mass transfer coefficient (MTC) significantly increases and ultrafiltration (UF) capacity decreases after 4 years on PD, with little effect on the urea MTC. Since the peritoneal equilibration test (PET) results usually mirror MTC results, the same findings would be expected in populations evaluated with PET. The increased transport characteristics suggest an increase in the effective peritoneal surface area and/or permeability due to diminished interstitial resistance over time. A 7-year follow-up study of patients on PD reported 23 patients who demonstrated increasing creatinine MTC and/or dialysate/plasma (D/P) creatinine after the third year [29]. Peritoneal rest for 4 – 12 weeks helped stabilize changes in MTC. Therefore, early recognition of transport alterations and peritoneal resting may allow a patient to continue on PD for longer periods of time. In a group of 90 patients with peritoneal membrane data tracked over 5 – 17 years, the creatinine MTC significantly increased over time concomitant with a decrease in UF capacity [97]. Urea MTC remained unaltered. Eighty percent of PD patients maintained stable solute transport characteristics, while 27% demonstrated an increase in back diffusion of solute and an increase in UF failure. Children may also develop membrane failure, especially after infection with Group A streptococcus.

Glucose dialysate modulates the function of mesothelial cells and peritoneal fibroblasts. In vitro exposure of peritoneal membrane cell lines can decrease proliferation rate, increase expression of profibrotic cytokine-transforming growth factor (TGF-β), metalloproteinases, advanced glycosylation end products, and fibronectin. Newer solutions (e.g. amino acid, icodextran, bicarbonate) may potentially "rescue" the peritoneal membrane from the fibrosis triggered by the above substances. An increase in transforming growth factor-β (TGF-β1), and an increase in collagen fibers with the generation of smooth muscle cells in the media may also play a role. Icodextran may extend PD usefulness by optimizing UF based on its molecular size. No effect was observed on permeability, but there was an increase in convective flow through the small pore system. UF failure due to a large effective peritoneal surface area may respond to icodextran. An alternative treatment option involves changing a patient to automated PD with short cycles.

A number of markers of peritoneal mesothelial cell function have been examined in an attempt to predict patients at risk for decreased membrane function over time. The dialysate effluent can provide valuable indirect information on the stability of the peritoneal membrane [42]. Cancer antigen 125 (CA^{125}), phospholipid and hyaluronic acid are produced by mesothelial cells, and CA^{125} levels reflect mesothelial cell mass or turnover. Although CA^{125} may not necessarily correlate with the actual number of mesothelial cells in the PD effluent, a decrease in CA^{125} in an individual patient reflects a decrease in overall mesothelial mass. In an attempt to preserve

Table 2. Approach to Ultrafiltration Failure*

History:	Onset, time on peritoneal dialysis, shortness of breath, weight gain, residual renal failure, drain pattern
Exam:	Location of edema: distal/central, pleural effusion, scrotal edema
Membrane characteristics:	Stable, increased, decreased
Diagnostic tests:	Serum albumin, plain radiographic exam (chest, abdomen), CT scan, CT with intraperitoneal contrast, radiolabeled scintigraphy
Treatment:	Peritoneal rest, surgical repair, cycler (APD), transfer to HD, phosphatidylcholine, heparin, alternate dialysate solutions†

*Ultrafiltration risk factors: time on PD, percent of dialysate glucose absorption, peritonitis rate, hyperosmotic dialysate frequency, impaired transcellular water transport, acetate dialysate, high intraperitoneal pressure.
† Short chain polypeptides, glucose polymer, amino acid, ultra-low sodium dialysate solutions.

the peritoneal membrane and avoid peritonitis, it may be important to avoid excess 4.25 g/dL dextrose, match modality with membrane transport, and avoid uncontrolled blood sugars or high glycosylated hemoglobin (HbA_1C > 8) [94]. The data are less clear regarding the optimal effective membrane resting period; the value of using intermittent vs. continuous PD; and the use of small-dose heparin surfactants, ADCON-D, mesothelial cell implantation, or addition of vitamin E or phosphatidylcholine to the dialysate.

Ultrafiltration (UF) Failure

UF failure can be classified as a true or an apparent loss of UF. The true loss refers more to specific membrane transport alterations, anatomical abnormalities, increase in lymphatic absorption, or catheter dysfunction. Apparent loss implies medical noncompliance, a mismatch between the transport characteristics and the prescription, loss from residual renal function or prescription noncompliance.

UF failure occurs in 6.2 – 11% of patients, and appears to increase with time spent on PD. After 6 years on PD, approximately 30% of patients may develop UF failure [57]. The approach to UF failure should consist of a clinical history, physical examination, characterization of membrane transport category, and an analysis of serum albumin (Table 2). Additional studies may include: plain X-ray of the chest and abdomen, computed tomography (CT) with or without intraperitoneal (IP) contrast, and radiolabelled scintigraphy. Typically, the net UF is > 400 mL in 4 hours using a 4.25% glucose dialysate (3.86%) solution.

UF failure can be categorized according to PET results (Table 3). Patients presenting with stable PET results may have catheter malposition, subcutaneous dialysate leak, or leak into the scrotal area with significant genital edema. Other etiologies for UF failure with stable PET test results include increased lymphatic absorption, increased intra-abdominal pressure and impaired transcellular water transport. While UF failure in PD is most likely not due to an increase in IP pressure,

Table 3. Usefulness of PET for Diagnosis of Ultrafiltration Failure in PD*+

PET Results (solute transport rate)	Possible diagnosis	Diagnostic Tests	Treatment
Increased (high)	Type I membrane failure	% glucose absorption	Short dwell times Peritoneal resting: 1 month ? alternate dialysate solution Avoid hyperosmotic dialysates (if possible)
	Peritonitis	Dialysate cultures	Aggressively treat peritonitis (antibiotic, heparin)
Stable (average)	Catheter malposition	X-ray	Surgical (laparoscopic, thoracoscopy, laparotomy)
	Dialysate leaks	CT with contrast scintigraphy technetium 99^{m} albumin	Surgical Alter dialyzing position
	Increased lymphatic reabsorption	Dextran, albumin+, exclusion	? phosphatidylcholine IP Transfer to HD
	Increased intra-abdominal pressure	IP pressure transducer ? rectal pressure monitor	Decrease volume
	Impaired transcellular water transport	D/P sodium (2 hours) UF with 1.5% vs. 4.25% glucose	Short dwell times Decrease % glucose ? transfer to HD
Decrease (low)	Type II membrane failure (sclerosing peritonitis)	Surgical exploration Peritoneal biopsy	Hemodialysis Catheter removal Prednisone /Imuran Tamoxifen ADCON
	Adhesions	Scintigraphy	Laparoscopic laser lysis ? tidal PD

* UFF in PD is defined as edema, inability to achieve dry weight with hypertonic exchanges (< 200 cc UF with 4.25% dilaysate). + Possible risk factors: time on PD,% dialysate glucose absorption, peritonitis rate, hyperosmotic dialysate frequency, impaired transcellular water transport, acetate dialysate, chronically high intraperitoneal pressure.

high IP pressures can decrease overall UF rates. For each 1 cm increase in water, there is a 70 mL decrease in UF after 2 hours. Patients with increased or high PET results may benefit from peritoneal resting or the use of alternate solutions, e.g. glucose polymer. Sclerosing peritonitis and adhesions should be considered as etiologies for a decreased or low PET result. Peritoneal resting is beneficial in these patients with peritoneal UF failure.

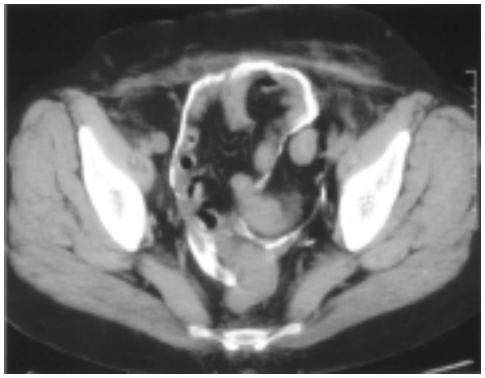


Figure 1a.

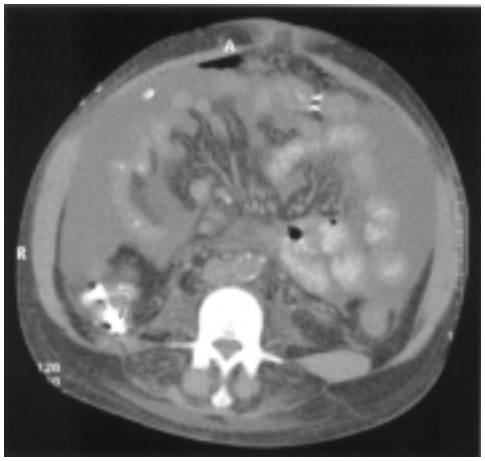


Figure 1b.

Figure 1. a: CT scan demonstrating a calcified peritoneum with centrally adherent bowel loops which conglomerate and lose the normal intestinal loop pattern (Courtesy, Burkhart, J.).
The normal intestinal distribution appearance is noted in Figure 1b.

Sclerosing Encapsulating Peritonitis (SEP)

A number of reports have described the development of SEP in continuous ambulatory peritoneal dialysis (CAPD) patients. The annual incidence rate is approximately 0.37/1000 patient-years. This rate may vary by country with 0.9 – 1.7% incidence in Japan, 0.7% occurrence in Australia, and 0.54% in Canada. While SEP is a rare complication, it is nonetheless serious and, in some cases, life-threatening. Depending on the study reported, there can be a predominance of either men or women with an increased occurrence after age 40 and after 4 years of PD [116].

For patients on PD more than 4 years presenting with abdominal pain, decreased UF capacity, progressive malnutrition (decreased weight), decreased serum albumin, anorexia, and blood stained effluent, SEP should be considered. The diagnosis can be made on the basis of a plain abdominal X-ray indicating obstruction, dilated small bowel loops, calcified peritoneum (Figure 1); abdominal ultrasound findings of matted bowel loops, an echogenic "sandwich" appearance around bowel loops with loculating ascites; CT indicating dilated bowel loops, loculated ascites, dense thickening of the peritoneal membrane, centrally adherent bowel loops which conglomerate with loss of normal intestinal loop pattern and luminal narrowing; or laparoscopy with peritoneal biopsy demonstrating inflammatory intra-abdominal infiltrates, dilated lymphatics, fibrotic thickening of the peritoneal membrane, and an absence of the mesothelial cell layer.

The multiple postulated etiologies for SEP include recurrent severe peritonitis, CAPD duration > 4 years, dialysate composition (acetate, hyperosmotic glucose, low pH), multiple abdominal surgeries, various drugs (β-blockers, disinfectants, IP antibiotics), and catheter foreign body. Mortality from SEP varies from 20 – 93%. A fatal outcome can occur in a significant percent of patients due to bowel obstruction, or complications from surgery and malnutrition. When surgery is employed for diagnosis or adhesion relief, special attention should be given to avoiding infection, optimizing nutrition with early total parenteral nutrition (TPN) and aggressive hemodialysis (HD) treatment.

Conservative treatment involves the removal of the PD catheter, transfer to HD and initiation of TPN to rest the bowel. Prednisone 30 – 50 mg/day and/or azathioprine 100 mg/day may help with overall patient outcome. Tamoxifen 20 mg every 12 hours orally (PO) for 6 – 12 months may decrease peritoneal membrane fibrosis in some patients. Newer substances to decrease adhesion formation (ADCON-D) may theoretically be helpful at the time of surgery. Transplantation may play a role in optimizing long-term outcomes.

Because most patients do not develop the risk for SEP until after a period of time on PD, screening tests may be useful in identifying individuals at increased risk for SEP. Changes in the morphology of the mesothelial cell appearance, abnormal peritoneal membrane function tests and typical findings on radiographic survey (e.g. CT scan, ultrasound) may be helpful.

Catheter-related Complications

A number of complications may be associated with the insertion of a PD catheter. Falcon et al.'s report indicated 27.6% of catheters develop a complication [33]. The complications include malposition (13%), dialysate leak (8.9%), hemoperitoneum (3.6%), peritonitis (1%), surgical wound infection (0.5%), and chylous ascites (0.5%). Recognizing risk factors and designing strategies to prevent leaks decreases the incidence of PD leak. Risk factors for these complications following insertion are previous abdominal surgery, particularly if it affected the peritoneal membrane; and early use of the catheter (< 5 days after implantation).

Catheter-related complications can result in catheter loss. The major causes for catheter loss are infection (80%), catheter defect (5%), PD failure (5%), drain failure (4%), and leak (3%). Overall catheter survival at one year is approximately 80%, decreasing to 50% by 3 years. The placement site, surgical technique, and use of perioperative antibiotics all play a role in avoiding early postoperative catheter-related complications. A paramedian incision is associated with the least complications. Furthermore, lower risk is observed when the catheter is fixed to the lower peritoneum with an additional suture. Several reports have delineated the benefit of inserting the peritoneal catheter 3 cm lateral to the linea alba, with placement of one purse-string suture fixed to the peritoneal membrane along the inner cuff, a second fixed on the dorsal fascia of the rectus muscle around the outer side of the cuff, and a third suture around the catheter in the ventral fascia [102]. Studies have not demonstrated a significant difference between bedside and standard surgical placement.

Standardizing laparoscopic placement may be helpful in improving long-term catheter survival. Centers may use a closed Verres needle technique or an open Hassan technique for the initial abdominal CO_2 gas insufflation. The smallest number of 3–5-mm ports should be made and 10- to 12-mm access ports should

be avoided. Ideally tight 2-layer closure should be performed. The post-laparoscopic leakage and herniation rates are dependent on access port placement position (lower abdominal quadrant), the number of ports, size (10-mm vs. 5-mm), closure (partial vs. full thickness), and time delay until the institution of PD. Fewer problems are observed with full fascial wound closure including the peritoneum.

A number of different catheters have been designed to optimize long-term catheter survival. These include the Oreopolus-Zellerman, Swan neck, Cruz catheter, Montcrief-Popovic catheter, and the Tenckoff single and double cuff catheters. Obese patients with a body mass index (BMI) > 40 kg/m^2 may benefit from using a presternal PD catheter consisting of 2 silicone rubber tubes formed by a titanium connector. Two-year catheter survival approximates 88%. The role of catheter configuration in the subsequent development of mechanical or infectious complications is unclear. Several reports comparing catheters with either single or double cuffs have demonstrated no significant differences in catheter survival, episodes of peritonitis, and exit site infection. Patients with the Swan neck catheters have a lower incidence of cuff extrusion and pericatheter leakage with better catheter survival, although the incidence of exit site tunnel infections and migrations is no better than with the standard Tenckoff catheter in some studies.

Peritoneal catheter dysfunction is a common complication of PD and a frequent source of morbidity, catheter loss, and additional cost of therapy. Inadequate flow occurs in 6 – 55% of catheters. Specific causes for catheter malfunction include intraluminal obstruction from blood, omentum, or fibrin; extraluminal obstruction from omentum, adhesions, catheter kinks, and constipation; and catheter migration with or without obstruction (Figure 2). Extraluminal obstruction and migration can result in one-way obstruction with slow infusion or drainage and abdominal pain with infusion or drainage. Catheter position may be assessed by a flat plate of the abdomen or CT peritoneography. Enemas, physical activity, higher dialysate inflow pressures, and catheter manipulation with a semiflexible wire under fluoroscopy may be helpful. Additional reported approaches include manipulation with a Fogarty catheter, laparoscopic re-positioning or open surgical exploration with omentectomy and pelvic suture tacking. In the setting of fibrin or a clot, it may be helpful to use urokinase or streptokinase 10,000 units in 2 mL injected into the catheter for 2 hours. Heparin 500 – 2000 units/L added to the dialysate may also provide some assistance. Preservation of the external tract in a dysfunctional catheter decreases time to catheter usage; otherwise, the catheter should be replaced.

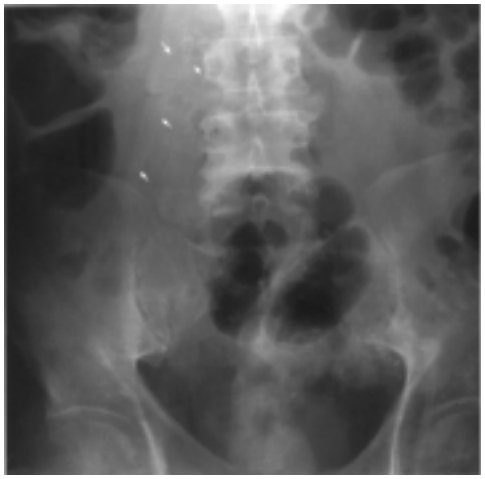


Figure 2. The arrows designate a peritoneal dialysis catheter which has migrated out of the pelvis and resulted in inadequate dialysis drain volumes (apparent ultrafiltration failure).

Both hernias and dialysate leaks may develop in patients following the placement of a PD catheter [7]. Several different types of

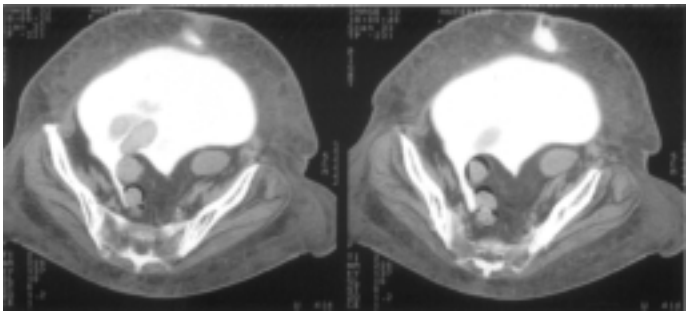


Figure 3. Computed tomographic peritonography delineates a subcutaneous pericatheter leak in a patient with ultrafiltration failure.

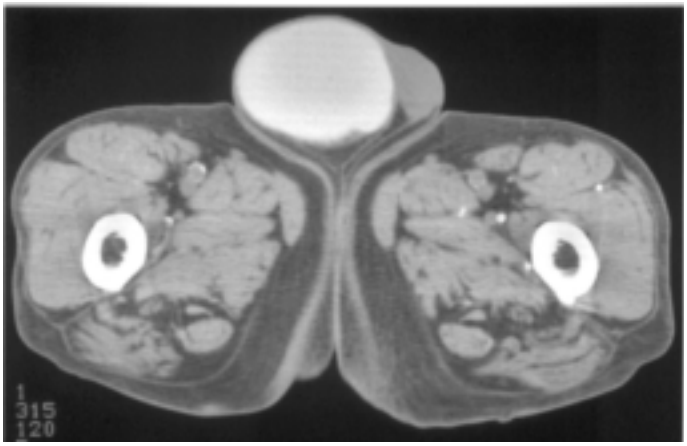


Figure 4. Scrotal edema in this male CAPD patient is characterized by the presence of contrast in the scrotal area which was secondary to a patent foramen vaginalis as seen on computed tomographic peritonography.

hernias may develop including internal cuff, umbilical, inguinal and/or incisional. A significantly greater incidence of hernia (inguinal, incisional, and umbilical) occur in autosomal dominant polycystic disease (ADPKD) patients on PD. Increased exchange volumes of 2.5 – 3 L is not associated with a significantly increased risk for hernia formation. The cycler is, however, associated with a decreased risk of hernia development due to the supine position for treatment.

All abdominal wall hernias should be repaired before PD is initiated to prevent progressive worsening. Consider 2 – 4 weeks of HD after hernia repair to minimize recurrence risks. If HD is not feasible, use supine intermittent low-volume dialysis for 2 – 4 weeks.

Dialysate leakage may occur at the exit site, in subcutaneous tissue (Figure 3), scrotum (Figure 4), labia, or pleural peritoneal (hydrothorax). The most common causes for scrotal edema are hernias and leaks along the catheter, or fluid overload. Catheter infection and peritonitis followed by a leak often lead to catheter loss and probably indicate an infection of the catheter's deep cuff. Infections developing following a leak usually resolve. Radionucleotide scanning, peritoneal scintigraphy with Tc^{99} M-colloid, and ultrasound may be helpful in identifying the site of leakage. Localization of leaks and abnormal IP collections by CT peritoneography are helpful if surgical management is contemplated. For early leakage, the treatment options include dialysis in the supine position with low volumes for 3 – 5 treatments, or transfer to HD for 1 – 2 weeks while withholding PD. A larger leak volume, malnutrition, and pa-

tient age > 80 correlate with a greater need for surgical repair.

Laparoscopic revision of a previous malfunctioning catheter may be complicated by dialysate leakage through the laparoscopic entry port. Restoration of an intact surface and an open defect in the peritoneum usually need 5 – 8 days of healing time, independent of the initial size of the defect. Increases in intra-abdominal pressure may delay abdominal wound healing by decreasing rectal sheath blood flow, resulting in tissue hypoxia. The early initiation of PD with 2-L volumes may contribute to this problem. Dialysate leak and hemoperitoneum have been observed after laparoscopic cholecystectomy in CAPD patients. Radionucleotide scanning, peritoneal scintigraphy with Tc^{99} M-colloid and ultrasound may be helpful in identifying the site of leakage.

Other reported catheter-related complications include omental herniation, pneumoperitoneum, erosion of the catheter into the mesenteric vessels, small bowel obstruction, and organ perforation: gall bladder, small bowel, large intestine, or bladder.

Hemoperitoneum

Hemoperitoneum (blood in the dialysate) may result from a large number of etiologies including: catheter-related splenic infarction, perforation of the gall bladder, amyloid bowel with perforation, exogastric leiomyosarcoma, hepatic angioleiomyoma, rupture of polycystic liver, rupture of hepatic tumor, ilioleiomyoma, carcinomatous liver, pericardiocentesis, retroperitoneal hematoma, menses, ruptured hemorrhagic ovarian cyst, giant multicystic hemangioma, perforated diverticulae and ischemic colitis. Wang et al. have characterized hemoperitoneum into 3 distinct groups [112]. Group I refers to benign retrograde bleeding from fallopian tubes, ovulation, catheter repositioning, femoral hematoma, immune thrombocytopenia purpura (ITP), warfarin, peritoneal entry after transplant, strenuous exercise, ectopic endometriosis, and use of hypertonic dialysate. Group II includes IP bleeding with significant pathology, usually persisting for > 36 hours, and characterized by a decrease in hematocrit (HCT) and blood pressure. Group II individuals may warrant laparotomy. Etiologies include pancreatitis, polycystic kidney disease with intracyst bleeding, postoperative bleeding and renal angiomyolipoma. Group III refers to significant bleeding requiring specified interventions. The etiologies include peritoneal laceration, ovarian cyst rupture, ruptured spleen or splenic artery, pseudoaneurysm, bowel perforation, or abdominal aortic aneurysm rupture.

Dialysis-related Pain Syndrome

Abdominal pain not related to infection may occur in the setting of PD. Once peritonitis is excluded, other etiologies should be considered including pancreatitis; cholecystitis; perforated ulcer or small bowel; ruptured diverticuli; incarcerated omentum; small bowel hernia; appendicitis; diverticulitis; mesenteric insufficiency; ischemic colitis; bowel infarction; and catheter erosion into vagina, bladder, or bowel. Patients on dialysis can develop a surgical abdomen independent of true peritonitis. Patients with persistent localized abdominal rebound, dilated loops of bowel, increased intra-abdominal air with pain, with multiorgan peritonitis or refractory peritonitis warrant consideration for surgical exploration. Dialysate infusion pain may result from conventional (40 mM) lactate dialysate. Bicarbonate and bicarbonate/lactate solution may decrease infusion pain. Rectal

pain with infusion may be related to the catheter being directed towards the posterior pelvis. If the pain does not resolve, the catheter may need manipulation or revision.

Infections

Overview of Peritonitis

Infectious complications represent the most important reason for patient drop-out from PD programs. The major sources of infection can be characterized into peritonitis and catheter exit site infection (CESI). As outlined in Table 4, gram-positive organisms (typically Staphylococcus species) are the most common cause of peritonitis and CESI, with gram-negative bacterial and fungal infections accounting for a lesser percentage. A wide variety of pathogens has been reported. Infections can occur via a number of different routes including intraluminal (touch contamination), periluminal (catheter tracking), transmucosal (via the intestinal wall, especially with acute constipation treatment and/or diarrhea), hematogenous, intra-abdominal, or via other loci (i.e. pulmonary, gynecologic, or urinary). The rate of sterile peritonitis may be as high as 20% depending on the culture technique (delayed culture inoculation, insufficient sample, initiation of treatment prior to culture, and atypical pathogens). Initial no growth peritonitis accounted for 14% of the episodes of peritonitis in the Network 9 Peritonitis and Catheter Survival study. Thirteen of 37 (35%) patients were positive with re-culturing (3 fungus, 5 gram-negative, 5 gram-positive) [13]. There was a greater percentage of patients over age 70 with gram-positive organisms, and patients who develop sterile peritonitis and place additives in their dialysate. Newer dialysis systems have decreased peritonitis risk. Optimizing dialysate sampling for culture is essential to the accurate diagnosis of peritonitis. Several traditional culture approaches are: standard culture of small amounts of dialysate; culturing large amounts with centrifugation, filtration, and removal of any antibiotics which may be present in the dialysate; a blood culture technique depending on lysis of leukocytes to increase the yield; and BACTEC, a radioactive culture technique.

Mycobacteria may be difficult to culture in certain settings. Patients with human immunodeficiency virus (HIV), hepatitis B (HBV), or active cytomegalovirus (CMV) infections, uncontrolled DM, or malnutrition are at increased risk for infection. A large number of case reports (Table 4) in the literature have delineated the broad spectrum of organisms (gram-negative and gram-positive bacteria, fungi, molds, parasites, and mycobacteria) responsible for infections in PD. *Penicillosis marneffei*, a newly emerging disseminated and progressive mycosis, will likely be seen increasingly in PD peritonitis in the future. There are significant differences in the course and treatment success depending on the type of organism.

Peritonitis

The diagnosis of peritonitis depends on the presence of abdominal pain and visibly cloudy fluid. Rarely, patients may present with abdominal pain out of proportion to the white blood cell (WBC) count, raising concerns for atypical mycobacteria, enterococci, fungus, or a more unusual organism. The total number of dialysate WBCs is usually > 100 cells/μL. The WBC differential may offer a

Table 4. Infection Complications by Organism

Organism	**Peritonitis**	% cases
Gram-positive[1]		50 – 75%
Staphylococcus aureus[2]	(40-50%)	
Staphylococcus epidermidis[2]	(40-60%)	
Streptococcal species	(3-15%)	
Enterococci	(3-10%)	
Gram-negative[3]		15 – 25%
Pseudomonas[4]	(5-10%)	
Non-*Xanthomonas*[4]	(10-15%)	
Fungus[5]		< 2%
Candida albicans	(75-80%)	
Non *C. albicans*	(20-25%)	
Other[6]		< 2%
Sterile		10 – 20%
Organism	**Catheter Exit Site**	% cases
Gram-positive		70 – 75%
S. aureus	(40-50%)	
S. epidermidis	(50-60%)	
Gram-negative		12 – 20%
Pseudomonas	(60-55%)	
Eschericae coli	(40-35%)	
Fungus		5%
C. albicans	(80-85%)	
Other	(15-20%)	

[1]Case reports: Rhodococcus equi, Bacillus cereus, Neisseria monocytogenes, Streptococcus pyogenes, Clostridium difficile, Nocardia asteroides. [2]Percent methcillin-resistant *S. aureus* and S. epidermidis are center dependent. [3]Case reports: Xanthomonas maltophilia, Agrobacterium radiobacter, Neisseria meningitidis, Capnocytophaga species, Moraxella (Branhamella) catarrhalis, Oligella urethralis, Pasteurella multocida, Acinetobacter, Neisseria cinerea, Aeromonas hydrophila, Flavobacterium, Alcaligenes xylosoxidans, CDC group EO-3, Neisseria sicca. [4]Escherichia coli, Klebsiella species, Acinetobacter, Enterobacter, Seuabia. [5]Case reports: Cryptococcus, Rhodotorula rubra, Aurobasidium pullulans, Histoplasma capsulatum, Trichosporon inkin. [6]*Parasites:* Giardia lamblia, Anisabis larva. *Mold:* Pennicillium species, Verticillium species, Aspergillus species, Biipolaris hawaiiensis, Exophiala jeanselomei, Fusarium species, Paccilomyces ravotii, Curvularia lunata (black mold), Aspergillus niger, Trichoderma gibrachiatum. *Mycobacterium:* tuberculosis, atypical mycobacteria (fortuitum, kansasii, gordonae, phlei)

Table 5. Empiric Therapy[1]

Treatment	Loading	Continuous Dose[1] (dose in each exchange)	Intermittent Dose[2] Administer in 1 exchange q day (dwell 4-6 hours) Residual Renal Function (cc/day) Anuria (< 500)	Non-anuria (> 550)
Cefazolin	500 mg/L	125 mg/L	500 mg/L	Increase dose by
Cephalothin	500 mg/L	125 mg/L	(15 mg/kg)	25%
Ceftazidime	250 mg/L	125 mg/L	1000 mg	1000 mg
Cefipime[6]	500 mg/L	125 mg/L	250 mg/L IP BID	
Gentamicin[3]	8 mg/L	4 mg/L	0.6 mg/kg body weight	0.6 mg/kg; IV/IP initial dose[7]
Tobramycin			See footnote for maintenance dose recommendations	
Vancomycin[4]	1000 mg/L (IP)	See footnote for maintenance dose recommendations[5]		
Aztreonam	1000 mg/L	250 mg/L	1000 mg/day	

Potential antibiotic regimens include: vancomycin + aminoglycoside, aztreonam or ceftazidime, cephalosporin + aminoglycoside, or cefipime

[1]Medications can be given IV or IP. Dosages are recommended for 1.73 m^2. [For patients with an increased risk for ototoxicity, use aminoglycoside alternative (aztreonam) plus vancomycin or cefipime alone.] Gentamicin plus cephalosporin can be given in the same exchange, dwell time 4 – 6 hours.

[2]Dose per drug level (dwell 4 – 6 hours). Due to decreased post antibiotic effect, once-daily dosing for cephalosporins may result in sub-optimal results.

[3]IV = 1.5 mg/kg; check level at 48 hours; redose intraperitoneally when level <2 mcg/L (Accurately document level prior to next dose as recommended)

[4]Check random level at 72 hours, redose when < 18 μg/L. For patients with RRF consider redosing in 3 – 5 days vs. 5 – 7 days in anuria.

[5]Indications for continued vancomycin dosing: PCN allergic, shock, methicillin resistant, not responding to standard treatment (check random level at 72 hours, redose when < 18 mg/ml)

[6]Use for broad spectrum coverage of gram-negative in place of ceftazidime and aminoglycoside.

[7]If administering with vancomycin, give vancomycin IP and aminoglycoside IV.

clue to the specific type of infection, with polymorphonuclear leukocytes (PMNs) being more common in bacterial peritonitis, while monocytes (> 10%) occur in fungal peritonitis, and increased lymphocytes may indicate an atypical infection such as mycobacterium. The presence of eosiniphils (> 100/μL) may indicate the usually benign con-

Table 6. Peritonitis Treatment Guidelines

Introduction

A. Reasons for re-assessing treatment
1. Increased number of vancomycin-resistant enterococci (VRE) in dialysis
2. Increased risk for VRE peritonitis
3. Risk of inadequate treatment regimens for peritonitis
4. Peritonitis related drop out patterns
5. Postantibiotic effect (PAE) vancomycin vs. intermittent cephalosporin
6. Hospitalization risk (> 50%)

B. Model protocols after Recommendations of the Advisory Committee on Peritonitis Management of the International Society for Peritoneal Dialysis 1996

C. Complete organism treatment sheet on all patients

D. Define benchmark peritonitis rate

Adapted from Keane et al.: Perit Dial Int, 1996, 16; 11.

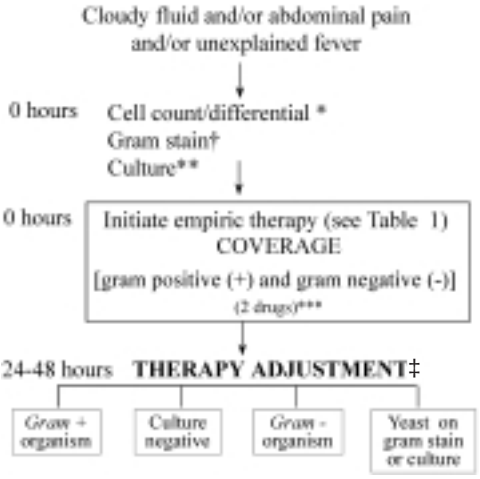


Figure 5. Initial Clinical Presentation with Peritonitis.
*Cell count > 100 cells/HPF (high power field) > 50% neutrophils suggest bacteria, > 10% monocytes suggest fungal, and lymphocytosis may indicate tuberculosis. †For a positive gram stain; intracellular organisms warrant rifampin if no contraindications exist. If yeast on gram stain, initiate antifungal treatment and await culture prior to removing catheter, unless patient's condition is deteriorating. **Culture technique (see text). ‡Check culture, verify sensitivity, adjust antibiotics (see text). ***Piperacillin or cefipime may replace ceftazidime in certain medical centers.

dition of eosinophilic peritonitis, although a fungal infection should also be considered. Eosinophilic peritonitis usually responds spontaneously, but low-dose prednisone has been used in persistent cases, with variable response.

A gram stain is positive only in approximately 20% of cases with peritonitis. Empiric treatment is usually begun after cultures are obtained. Figure 5 summarizes empiric therapy and subsequent adjustment after culture results are known, typically 24 – 48 hours. Both gram-positive and gram-negative organisms should initially be covered unless the infection represents a documented relapse. Patients who require continued vancomycin

Table 7. Dosages for Some of the More Frequently Used Antibiotics

Drug	Dosing	
	Intermittent (1 dose/day unless otherwise specified)	Continuous (mg/L unless otherwise specified)
Aminoglycosides		
Amikacin	2 mg/kg	LD 25, MD12
Gentamicin[1]	0.6 mg/kg	LD 8, MD 4
Netilmicin	0.6 mg/kg	LD 8, MD 4
Tobramycin[1]	0.6 mg/kg	LD 8, MD 4
Cephalosporins[2]		
Cefazolin	15 mg/kg	LD 500, MD 125
Cephalothin	15 mg/kg	LD 500, MD 125
Cephradine	15 mg/kg	LD 500, MD 125
Cephalexin	500 mg PO QID	NA
Cefamandole	1000 mg	LD 500, MD 250
Cefepime	250 mg BID	LD 500, MD 250 (BID)
Cefmenoxime	1000 mg	LD 100, MD 50
Cefoxitin	ND	LD 200, MD 100
Cefuroxime	400 mg PO or IV	LD 200, MD 100-200
Cefixime	400 mg PO	NA
Cefoperazone	ND	LD 500, MD 250
Cefotaxime	2000 mg	LD 500, MD 250
Cefsulodin	500 mg	LD 50, MD 25
Ceftazidime	1000 mg	LD 250, MD 125
Ceftizoxime	1000 mg	LD 250, MD 125
Ceftriaxone	1000 mg	LD 250, MD 125
Penicillins		
Azlocillin	ND	LD 500, MD 250
Mezlocillin	3000 mg IV BID	LD 3000 mg IV, MD 250
Piperacillin	4000 mg IV BID	LD 4000 mg IV, MD 250
Ticarcillin	2000 mg IV BID	LD 1000-2000 mg IV, MD 125
Ampicillin	ND	MD 125; or 250-500 mg po BID, 250-500 mg po QID.
Dicloxacillin	ND	MD 125
Oxacillin	ND	MD 125
Nafcillin	ND	250-500 mg PO every 12 hours
Amoxacillin	ND	
Quinolones		
Ciprofloxacin	500 mg PO BID	Not recommended
Fleroxacin	800 mg PO loading, then 400 mg PO daily	Not recommended
Ofloxacin	400 mg PO loading, then 200 mg PO daily	Not recommended
Others		
Vancomycin	15 – 30 mg/kg for 5 – 7 days	LD 1000, MD 25
Teicoplanin	400 mg IP BID	LD 400, MD 40[a]
Aztreonam[3]	1000 mg	LD 1000, MD 250

Table 7. continued

Drug	Dosing	
	Intermittent (1 dose/day unless otherwise specified)	Continuous (mg/L unless otherwise specified)
Clindamycin	ND	LD 300, MD 150
Erythromycin	500 mg PO QID	LD ND, MD 150
Metronidazole	500 mg PO/IV TID	ND
Minocycline	100 mg PO BID	NA
Rifampin	450-600 mg PO daily or 150 mg IP TID-QID.	NA
Antifungals		
Amphotericin	NA	1.5
Flucytosine	1000 mg daily PO or 100 mg/L IP each exch x 3 days, then 50 mg/L/exch 200-8000 mg PO	50
Fluconazole	ND	ND
Ketoconazole		NA
Miconazole		LD 200, MD 100-200
Combinations		
Ampicillin/sulbactam	2000 mg every 12 hours	LD 1000, MD 100
Imipenem/ciliastatin	1000 mg BID	LD 500, MD 200
Piperacillin/tazobactam[4]		
Trimethoprim/sulfamethoxazole[5]	320/1600 mg q. 1 – 2 days PO	LD 320/1600, MD 80/400

The route of administration is intraperitoneal (IP) unless otherwise specified. The pharmacokinetic data and proposed dosage regimens presented here are based on published literature reviewed through January 1996. There is no evidence that mixing different antibiotics in dialysis fluid (except for aminoglycosides and penicillins) is deleterious for the drugs or patients. Do not use the same syringe to mix antibiotics.
[a]This is in each bag x 7 days, then in 2 bags/day x 7 days, and then in 1 bag/day x 7 days.
LD = loading dose; MD = maintenance dose; NA = not applicable; ND = no data; IV = intravenous; IP = intraperitoneal; PO = oral; BID = twice a day; TID = three times a day; QID = four times a day

NOTE: CAPD patients with residual renal function may require increased doses or more frequent dosing, especially when using intermittent regimens.
[1]Levels should be obtained to guide dosing interval. Consider redosing when level falls < 2 μg/L
[2]Concerns exist regarding lack of post-antibiotic effect
[3]Can be utilized for penicillin-allergic patients
[4]Zosyn (piperacillin/tazobactam) replaces timentin for serious polymicrobial nosocomial infections. Adapted from Keane et al. Perit Dial Int 1996;16:561
[5]Stenotrophomonas is uniquely sensitive to trimethoprim/sulfamethoxazole

need drug level determinations to maintain a serum level of > 18 μg/mL, especially in patients with residual renal function. Trough vancomycin levels may predict the risk for relapse of gram-positive infections. A low 4-week main trough (< 12 μg/mL) or initial 7-day trough (< 14 μg/mL) vancomycin level indicates an increased risk for subsequent peritonitis relapse. Dosing intervals of approximately every 5 days (patients without residual renal function) and 3 – 4 days (residual renal function patients) are needed to achieve therapeutic levels. Table 7 lists dosages for commonly used antibiotics. A new class of antibiotics, the oxazolidinones, may offer increased effectiveness against methicillin-resistant *Staphylococcus aureus* (MRSA).

Even though *Staphylococcus epidermidis* is the most common touch contamination pathogen, the frequency of infection from more virulent S. aureus has increased dramatically in some centers. Patients with nasal carriage of *S. aureus* are at increased risk (4 – 6.7 times that of non-carriers) for the development of *S. aureus* CESI and/or peritonitis. While patients with gram-negative peritonitis respond to appropriate antibiotic treatment, pseudomonal infections, especially CESI, are difficult to cure. Early and aggressive therapy is essential because of significant morbidity. Prevention, including disinfecting showers and soaking shower heads with sodium hypochlorite, and disinfecting areas with stagnant water, is the key to decreasing the incidence of outbreaks.

Maneuvers which alter bowel mucosa and/or cause diarrhea increase the risk for gram-negative infection. These include enemas, frequent suppositories, alternating constipation/diarrhea, diabetic colon dysfunction, *Clostridia difficile* diarrhea and H_2 blockers. The majority of fungal infections are due to *Candida* species usually after antibiotic treatment, malnutrition, or with additional risk factors (e.g. DM with esophagitis). Percutaneous endogastrostomy tube placement and surgical jejunostomy in patients with diabetic gastroenteropathy and malnutrition may pose an increased risk for fungal peritonitis. Mycobacterial peritonitis should be considered in patients with apparent sterile peritonitis and lymphocyte predominance. A peritoneal biopsy may be warranted to increase the diagnostic yield. A number of different atypical mycobacterial species have been reported in addition to several different types of mold.

A disciplined approach to peritonitis treatment is essential to optimize outcome and maintain patients on long-term PD. While a number of different treatment approaches utilizing IV, PO, or IP medications have been proposed, a reasonable approach is presented in Figures 6 – 10. From 1993 to 1996, the Peritonitis Working Group shifted the emphasis from vancomycin and ceftazidime to cephalosporin and gentamicin in response to concerns regarding vancomycin-resistant enterococci (VRE). The emergence of VRE in dialysis units has raised critical international health concerns. The major concern relates to the potential for the transfer of the vancomycin resistance (genes) from VRE to other gram-positive organisms such as *Staphylococcus*. Clinical isolates of vancomycin-resistant pneumococci have now been identified. The enterococci species are now the second most frequent cause of nosocomial infections in the US and are increasing in their resistance to vancomycin. The larger the hospital, the greater the percent of resistant enterococci. With < 200 patients the percent of resistant enterococci is 0.6%; this increases to 7.2% with > 500 patients. Patients presenting with VRE are more likely to be malnourished, > 40 years old, have gastrointestinal (GI) abnormalities such as diarrhea and incontinence,

and have a prior history of antibiotic use. Seemingly a single dose of vancomycin should not significantly increase the risk for VRE, but continued use of vancomycin for any subsequent dose when other antibiotics are appropriate is discouraged. Therefore, treatment with vancomycin is reserved for serious infections with hemodynamic compromise, patients with documented allergies to penicillin, and prophylaxis when there is a high incidence of MRSA or methicillin-resistant *S. epidermidis*.

Appropriate use of cephalosporins is also crucial, given their increased use. Several points should be made regarding the use of cephalosporins and aminoglycosides as empiric treatment. Cephalosporins need to be administered in each exchange due to their lack of negative post-antibiotic effect. While some work has described the use of a high daily dose, further study is needed to validate this dosing scheme. Proper dosing of aminoglycosides should be guided by serum levels, although appropriate drug levels do not guarantee against toxicity. Patients who have an increased risk for aminoglycoside toxicity (e.g. diabetics, patients with prior aminoglycoside dosing in the previous 2 months, and individuals with subclinical hearing deficits) should be identified and alternate treatment protocols designed.

The routine use of IP heparin does not appear to affect the overall outcome of peritonitis. Several reports have utilized heparin, urokinase or streptokinase in cases where there is significant fibrin formation during the course of infection. Fibrin may harbor microorganisms and lead to dialysate drain problems.

Gram-positive organisms (Figure 6) can be divided into 4 different categories: enterococci, *S. aureus*, MRSA, and VRE. For *S. aureus* infections, a 21-day course of therapy is indicated. In diabetic or malnourished individuals, prophylactic coverage for fungal infection should be initiated using mycelex trouches, nystatin oral suspension, diflucan or clotrimazole vaginal cream in female patients. If VRE is documented, the patient will most likely be switched to HD and subsequent antibiotic treatment with quinupristin/dalfopristin, chloroamphenical or trimethoprin-sulfamethoxazole (TMP-SMX) employed.

When gram-negative organisms are identified, the antibiotic selection (Figure 7) should be based upon whether there is a single gram-negative (non-xanthomonas) or either *Pseudomonas* or *Stenotrophomonas*. Gram-negative organisms can be classified into oxidase-negative and oxidase-positive infections or lactose-positive. In the setting of pseudomonal infections, 2 drugs are essential for eradication; TMP-SMX is the primary medication used for *Stenotrophomonas*. Aminoglycoside agents should be continued for *Pseudomonas* infections if there is not a significant risk for vestibular ototoxicity.

If yeast is identified on gram stain and culture, the PD catheter should be removed and the patient should be treated with amphotericin and/or fluconazole depending on culture results (Figure 8). Although catheter salvage with treatment has been reported, the course is protracted and may pose significant patient morbidity. Fluconazole may be effective in healthy, well-nourished dialysis patients; however, certain patients not responding to fluconazole should be switched to IV amphotericin even though the organism may be sensitive to fluconazole in vitro. Delay in converting patients not responding to fluconazole and with persistence of abdominal pain and positive gram stain will lead to increased morbidity and mortality.

Patients presenting with multiple organisms and/or enterococcal infections should be treated appropriately with gram-negative, gram-positive, and/or anaerobic coverage. If

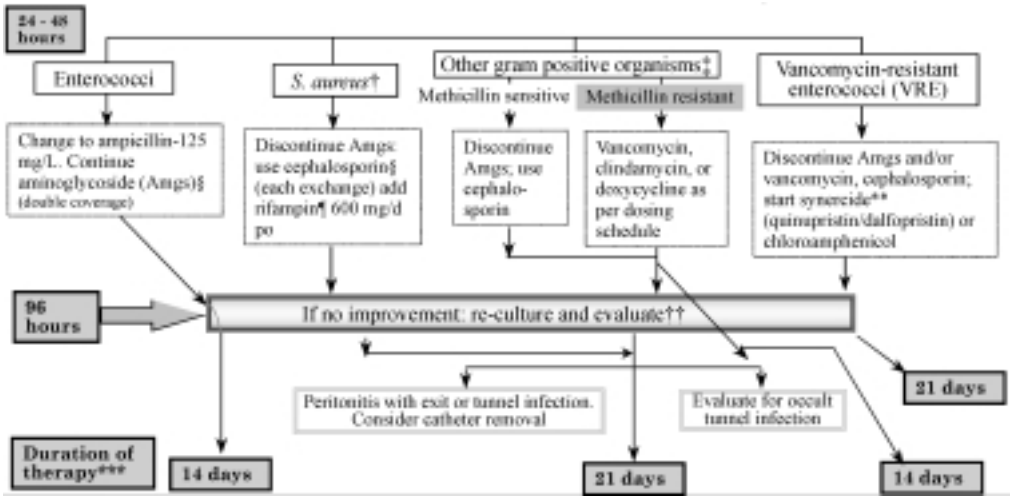


Figure 6. Treatment Algorithm for Gram-positive Organism on Culture. Choice of therapy should always be guided by sensitivity patterns. Avoid prolonged vancomycin use. † If enterocci is resistant to aminoglycoside, use ampicillin alone. ‡ PCN-allergic alternative agents: vancomycin, clindamycin, rifampin, quinolones (ciproflocaxin or ofloxacin). If not PCN-allergic, use anti-staph or 1st generation cephalosporin; if anaphylactoid reaction, use vancomycin. ¶ Ensure normal liver function tests and **NO** lens implants. **Synercide intraperitoneal 1 to 1.5 grams IP in 4 – 6 hours dwell, chloroamphenicol IV 500 mg q 6 hours. †† If methicillin-resistant *S. aureus* is cultured and the patient is not responding clinically, vancomycin or clindamycin plus rifampin should be used. ***Add mycelex trouches for diabetic patients or when total antibiotic treatment > 14 days. Dose mycelex trouches one qid, nystatin (oral suspension) 500,000 IU qid, or diflucan 100 mg qd for entire treatment plus 5 days. For female patients with yeast vaginal infections, use gyne-lotrimin to decrease risk of vaginal candidiasis seeding.

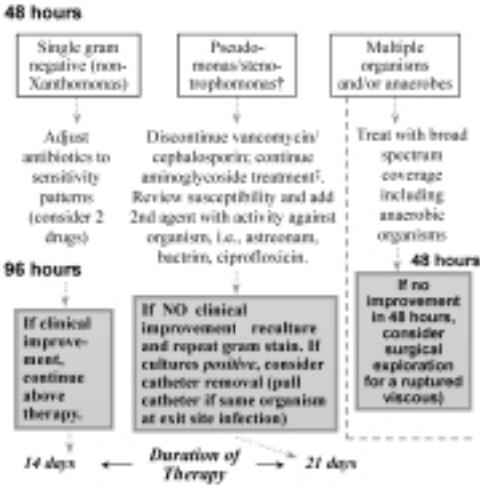


Figure 7. Approach to Gram-negative Organism or Polymicrobial. *(a) Lactose (–)oxidase (–): *Proteus mirabilis, Proteus vulgaris, Providencia* species, *Morganella morganii, Serratia, Salmonella, Shigella, Acine tobacter, Stenotrophomonas*. (b) Lactose (–) oxidase (+): *Pseudomonas aeruginosa, Aeromonas hydrophilia, Moraxella* species, Alcalignes, *Flavobacterum* species, *Hemophilus influenzae*. For *Flavobacteruim*, vancomycin ist the drug of choice. (c) Lactose (+): *E. Coli, Klebsiella, Enterobacter, Citrobacterium*. †For *Pseudomonas* use 2 drugs; for *Stenotrophomonas*, use 1 medication (e.g. trimethoprim-sulfamethoxazole). ‡Continue aminoglycoside unless significant risk for vestibular-ototoxicity. §Cell count **not** decreasing, symptoms persist.

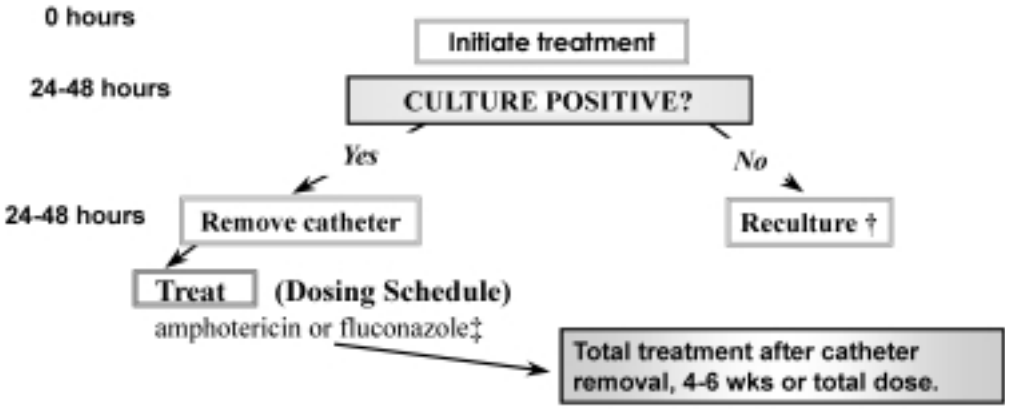


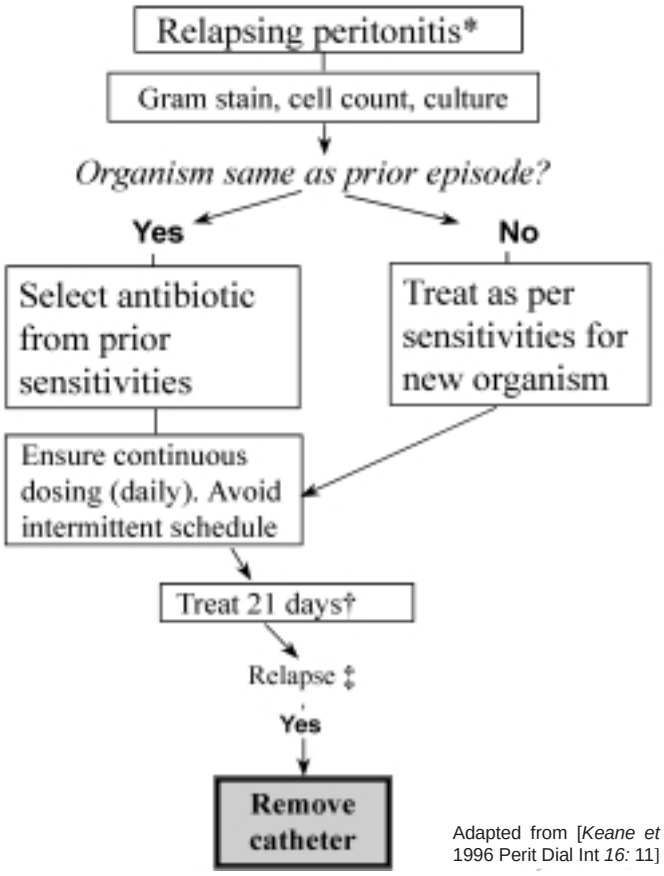
Figure 8. Approach to Fungal Infection in PD – Yeast on Gram Stain (Should see increased % monocytes, significant pain/symptoms) †If symptoms increase and monocytes > 20%, check for acid-fast bacilli. ‡Use fluconazole (200 mg LD, PO then 100 PO daily × 14 days) if Candida albicans; use amphotericin for all other sensitive fungus: total treatment dose IV ≥ 250 mg. Use test dose prior to standard treatment (1mg) dependent on organism sensitivity and infection resolution. A new PD catheter can be inserted in 4 – 6 weeks. Fluconazole may not be as effective as amphotericin, and should be used primarily in healthy, well-nourished dialysis patients. If patient is not responding with fluconazole, convert to IV amphotericin for total treatment course.

there is no improvement in the cell count and clinical status within 72 hours, the patient should undergo surgical exploration because of the high likelihood of a ruptured viscous. While IP free air can be observed on plain films of PD patients, excessive amounts in the setting of persistent infection should raise the possibility of a ruptured viscous. A delay in surgical intervention will lead to a poor outcome in these individuals. Eighty percent of patients developing polymicrobial infections can remain on PD if aggressively treated; the other 22% require catheter removal and transfer to HD.

Abdominal abscesses may complicate peritonitis in CAPD patients, with an incidence of abscess development in 0.7% of peritonitis episodes. Persistent symptoms, IP leukocytosis and culture positivity should prompt a CT abdominal/pelvic evaluation for abscess formation. Draining of the abscess percutaneously or via open surgical procedure will improve the overall patient outcome.

Relapsing peritonitis (Figure 9) is defined as an infection by the same organism < 21 days after treatment. Optimizing sampling and culturing techniques is essential for organism identification. The infection should be treated based upon sensitivities for at least 21 days. Sequential C-reactive protein (CRP) levels have been suggested as a guide for duration of treatment. If a patient relapses with the same organism after a second treatment course, consideration should be given to catheter removal.

Patients utilizing automated PD may present antibiotic dosing dilemmas. Factors that may lead to suboptimal treatment include IP dosing with short dwell times; inappropriate drug levels; low peak to minimal inhibitory concentration (MIC) levels; a short duration of serum levels that exceed MIC or minimal bactericidal capacity (MBC) (intensity index); and delay in conversion to CAPD when IV, IP or PO routes of administration are not effective or practical.



Adapted from [*Keane et al* 1996 Perit Dial Int *16:* 11]

Figure 9. Treatment Approach to Relapsing Peritonitis. *Same organism < 21 days post treatment, recurrent infection: < 21 days with same organism. †Obtain negative culture, normal CRP prior to stopping therapy, add mycelex trouches for duration of treatment and 7 days thereafter. ‡Third bout same organism. If different, individualize therapy; if same proceed to catheter removal.

Catheter Exit Site Infection (CESI)

The rates of CESI and the outcomes of treatment are inconsistent in the literature. Rates may vary from as low as 0.1 – 0.5/patient-year to as high as 1.02/patient-year. This discrepancy may reflect differences in the definition of CESI, chronic and acute care protocols, and treatment of infection once diagnosed. More than 10% of catheter losses occur with CESI. The most common clinical scenarios which result in catheter removal are: the same organism causing CESI and peritonitis, recurrent peritonitis (> 3 episodes same organism), fungal peritonitis, peritonitis with multiple organisms, infection persisting > 3 weeks despite adequate therapy, involvement of the internal cuff documented by ultrasound which has not improved (persistence of peri-cuff fluid) despite antibiotics, and abdominal abscess formation. Both race and climate-specific characteristics may affect infection rates; there is an increased incidence in CESI in tropical climates. Twardowski et al. established 7 different categories of CESI: acute, chronic, external-cuff, equivocal, good, perfect, and traumatized [107]. Table 8 characterizes 4 different CESI categories. The outcome of catheter-related infections depends on the causative organism and degree of inflammation. A significant difference exists

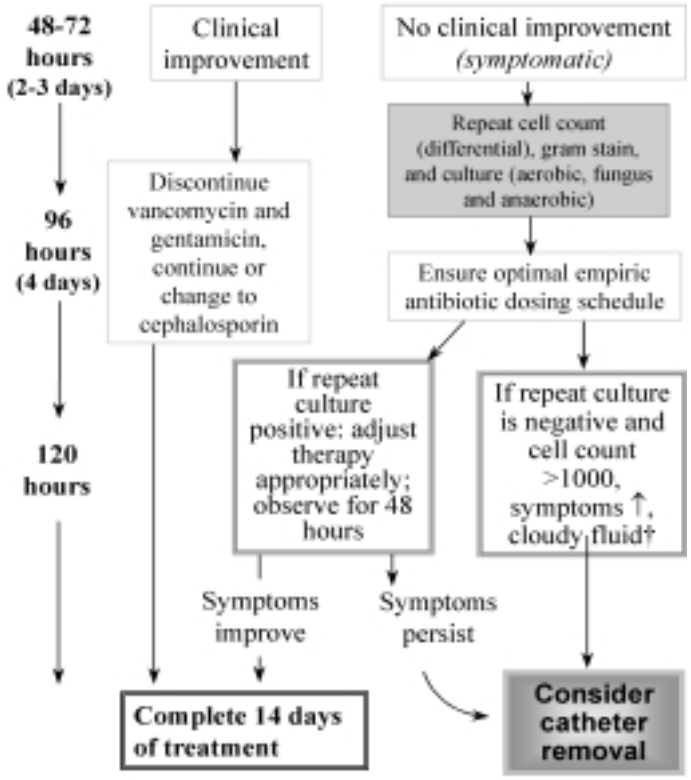


Figure 10. Approach to Culture-negative* Peritonitis. *Consider chemical peritonitis (check for eosinophils; eosinophilic peritonitis, increased cell count with the exclusion of aerobes, anerobes, and fungus). †Discuss with primary nephrologist, consider fungus, acid-fast bacilli, mold (monocytes on differential), or incompletely treated bacterial infection.

between true exit site infections and exit site combined with tunnel/cuff involvement.

Acute infections usually are < 4 weeks in duration, and cause painful erythema at the exit site with a visible sinus tract and usually purulent or bloody external drainage. The acute infection necessitates the cauterization of granulation tissue, and hypertonic saline soaks may improve drainage if purulence is present. When copious purulent drainage occurs, dressings should be changed twice a day. Systemic antibiotics should be empirically started pending culture results if there is a high level of clinical suspicion. The antibiotics may subsequently be adjusted according to the culture and sensitivities. Local antibiotic ointment or solution cannot achieve adequate tissue levels and are usually not effective. Oral cephalosporins or a quinolone (ciprofloxacin 500 – 700 mg/day) may be the initial antibiotics of choice. Exit site infections should be treated for 7 days after there appears to be catheter exit site improvement, with total treatment lasting approximately 10 – 14 days.

Chronic exit site infections have inflammation > 4 weeks. These infections are usually characterized by purulent or bloody external drainage usually greater in amount than during the acute infection phase (Figure 11). Purulence is typically apparent on the dressing. Chronic infections usually lack induration and erythema. Acute changes may occur with trauma, abscess, external cuff seeding, or a second or new organism. Compulsive exit-

Table 8. Management of Catheter Exit Site (CES) Infectious Complications[1]

Classification	Acute (< 4 weeks)	Chronic (> 4 weeks)	Tunnel/cuff infection	Trauma
Appearance	Usually painful erythema > 13 mm, visible sinus tract, purulent or bloody external drainage, possible crust	Widening induration > 13 mm, crust positive, usually sinus tract, (+) dressing drainage, may see proud flesh	Pain over cuff or along tunnel without scab or crust, thick, "gluey/gooey" discharge especially with external cuff	Painful, may have bloody drainage, may be tender over cuff
Diagnosis	Exam culture, gram stain	Exam, culture[2], gram stain, cuff/tunnel ultrasound[3],	Exam, culture, gram stain, ultrasound, cuff/tunnel	History and exam
Exit site management	Cauterize (silver nitrate) granulation tissue, 3% hypertonic saline soaks 5-10 min TID local care: non-ionic surfactant cleansers[4], change dressings BID for significant drainage	Cauterize (silver nitrate) granulation tissue, 3% hypertonic saline soaks 5-10 min TID local care: non-ionic surfactant cleansers[4], change dressings BID for significant drainage	3% hypertonic saline soaks 5-10 min TID, dressing change bid; for copious drainage, may need absorbent dressing, consider unroofing or cuff shaving if external cuff involved	Daily exit care, utilize dressing, use non-irritant cleansers qd
Antibiotic[5]	Start systemic antibiotics, before culture results, adjust when culture sensitivities are available. Treat for 7 days after CES improvement	Utilize synergistic therapy. If standard treatment not successful in 2 weeks, change antibiotics, consider chronic suppressive therapy	Start systemic antibiotics, adjust therapy based on sensitivities and exam	Quinolone or cephalosporin for 5 to 7 days at the time of exit site injury.

(continued on next page)

site local care utilizing hypertonic saline along with cauterization with silver nitrate of granulation tissue is essential. Patients may require synergistic therapy for eradication once the organism is identified. If there is suboptimal response or no change in 2 weeks, antibiotic regimens should be reassessed.

Tunnel or cuff infection pain occurs directly over the cuff or along the tunnel without scab or crust formation at the catheter exit site. The purulence is characterized as gluey or gooey, being thicker than that usually seen with acute inflammation. In some settings, pressure on the cuff will express purulent drainage not apparent at the initial inspection. The outcome of cuff infections is poor despite unroofing and cuff removal. Tunnel infections involving the Dacron cuff are rarely completely cured,

Table 8. continued

Classification	Acute (< 4 weeks)	Chronic (> 4 weeks)	Tunnel/cuff infection	Trauma
Follow-up	Clinic visit every week until improved	Clinic visits every 2 weeks until improved. If drainage persists with induration, consider catheter removal[6]	Evaluate weekly dependent on drainage amount and appearance. Consider cuff un-roofing, cuff shaving if no improvement	Evaluate one week post trauma or sooner if exit site appearance changes

[1]Risks for infectious exit site complications: postoperative hematoma at CES, diabetes mellitus especially with poor glucose control, obesity, positive *S. aureus* nasal carrier, early *S. aureus* infection, early trauma (< 4 weeks post placement) with pain over cuff, dialysate leak at CES, upward exit site, infection < 2 weeks after placement without perioperative antibiotics, gross CES contamination (stagnant or contaminated water). [2]Cultures may be negative if on antibiotics. [3]Povidone iodine (betadine) inactivated by purulent drainage. [4]Examine for pericatheter somnolucent fluid collection (hypoechoic area). [5]Duration of therapy depends on response: cephalosporin for gram positive, quinolone for gram-negative, vancomycin IV or IP for MRSA. If treatment > 2 weeks add fungal prophylaxis: vaginal clotrimazole cream, mycelex trouches, or fluconazole (low-dose). [6]Indications for catheter removal: resistant *Pseudomonas* infection, peritonitis same organism as CES, CES infection with persistent leak, persistent erythema and tunnel infections with positive internal cuff by ultrasound. Modified from Twardowski and Prowant, 1997.

although catheter life can be prolonged with external cuff shaving and systemic antibiotics. Especially in patients awaiting transplantation, it is critical to aggressively treat and document lack of cuff involvement and resolution of tunnel edema. Ultrasound may be helpful in evaluating the internal or deep cuff, and appears to be better than WBC scanning in identifying tunnel infections. Hypoechogenicity indicating a fluid collection, > 2 mm in width along any portion of the catheter track is problematic. Several reports have now demonstrated the usefulness of ultrasound looking for a pericatheter sonolucent fluid collection in the area of the cuff as a predictor of catheter loss, with a higher incidence of detection of tunnel infections (0.35 episodes/patient-year with ultrasound compared with 0.12 episodes/patient-year by clinical criteria). If there is a significant decline of the hypoechoic area around the cuff, then chances are greater for recovery. If there is a decline of < 30%, the vast majority of catheters will be lost. Plum et al. noted that no patient with a negative ultrasound examination underwent surgery for infectious complications, while 69% of catheters with tunnel inflammation on sonographic examination had to be removed [86]. When the ultrasound indicated a tunnel infection, peritonitis rate was significantly higher: 1.7 episodes/patient-year vs. 0.64 episodes/patient-year.

Both the type of cultured organism and the extent of inflammation (i.e. involvement of internal cuff segment) are prognostic factors for the outcome of infection. Because of the indolence in morbidity of *S. aureus* site infections, these patients should undergo sonographic evaluations to determine the level of involvement and chance for eradication. *S.*

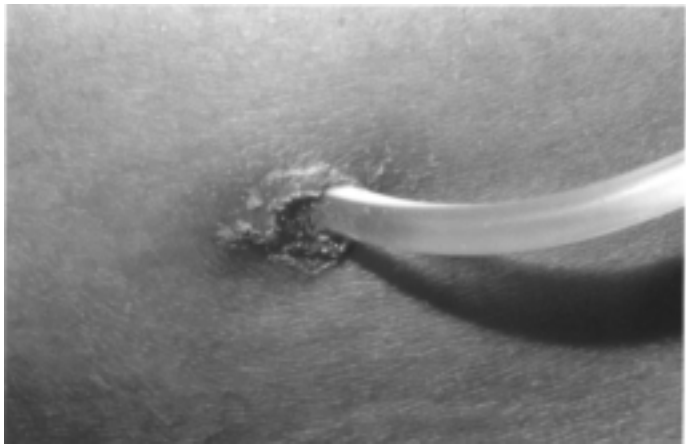


Figure 11. This chronic catheter exit site infection is characterized by persistently purulent external drainage with little or no induration and erythema.

aureus and *Pseudomonas* infections are the most serious infectious organisms causing chronic inflammation and/or eventual catheter removal.

Traumatized exit sites are usually noted by patients due to pain and bleeding, or a change in exit site appearance. Since infections can occur in 2 – 4 days, patients should be started on antibiotics and daily non-irritant cleansers. Quinolones or cephalosporins may be started at the time of injury and continued for 5 – 7 days to decrease the risk of cuff infection and catheter loss. Patients with acute, chronic, or tunnel infections, or trauma should be followed closely until resolution.

Subcutaneous cuff removal in persistent exit site or tunnel infections can significantly reduce catheter loss related to infection. If partially exposed or palpable within 3 cm of the exit site, the cuff may by removed by blunt dissection under local anesthesia at the bedside (Figure 12).

A number of local care antiseptic solutions (hypertonic saline, povidone iodine, sodium hypochlorite, chlorhexidine, dilute hydrogen peroxide) have been used to resolve or prevent CESI. With hypertonic saline therapy, 4 – 5 gauze pads soaked with warm 3% saline are applied 3 times daily for 5 – 10 minutes for 2 – 4 weeks followed by once daily thereafter. Several reports have examined the use of chlorhexidine vs. povidone iodine and noted a significant decrease in the frequency of CESIs with the former treatment. Povidone iodine ointment or cleanser offers some protection against CESIs, but the benefit is apparently limited to approximately 140 days following the start of PD and may be neutralized if an acute infection with purulent discharge develops [111]. Twenty-three to 45% of cases using povidone iodine turned positive for microorganisms within 24 months. *S. aureus*, *S. epidermidis* and *Pseudomonas* are the most common organisms seen. Alternating the catheter exit site care in patients at risk especially after 3 – 4 months of povidone iodine would be a reasonable option. Sodium hypochlorite and sodium chloride are effective against a broad spectrum of organisms (including *S. aureus* and *Pseudomonas*) with rapid killing in one minute and prevention of reinfection. Partial electrolysis of sodium chloride (Amuchina) to eliminate sodium hy-

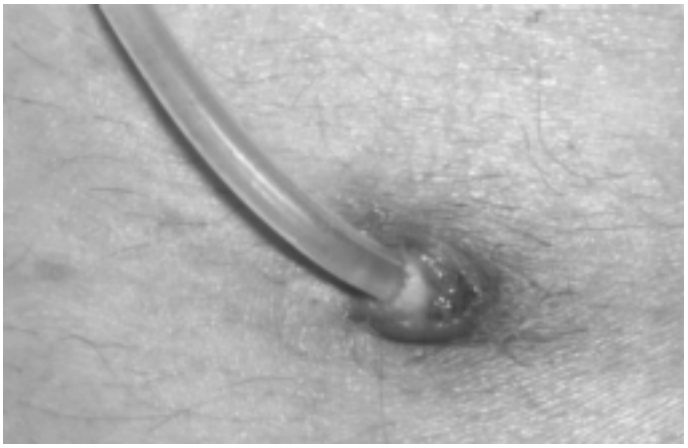


Figure 12. An infected, partially exposed Dacron cuff can result in recurrent or non-healing catheter exit site infections. The cuff can be removed at the bedside with blunt dissection under local anesthesia.

droxide may increase efficacy and decrease the toxicity of standard sodium hydrochlorite.

Antibiotic selection is crucial in all these types of infections. A Consensus Committee of the International Society of Peritoneal Dialysis on peritoneal catheter and exit site practices towards optimum peritoneal access (1998 update) [34] noted that in patients with gram-positive organisms, oral penicillinase-resistant penicillins, cephalexin, or TMP-SMX should be utilized. Unless a patient had a history of MRSA, vancomycin should be avoided. In *S. aureus* infections, rifampin 300 mg twice daily (BID) in adults or 5 – 10 mg/kg BID in children should be administered. With gram-negative infections, ciprofloxacin 500 mg BID should be used until the exit site is normal. The outcome with ciprofloxacin for the treatment of CESI was significantly better than with other antibiotics with a mean recovery of nearly 50%; however its use is contraindicated in children. IV and IP treatment can be considered if the resolution is slow with PO treatment.

In patients with mycobacterial, pseudomonal, or xanthomonal infections, differences may exist in the subsequent risk for peritonitis and catheter removal. *Xanthomonas*, although associated with other microorganisms in 66% of cases, is less likely to lead to peritonitis and catheter replacement than pseudomonal CESIs, which are usually severe and require IV or IP antibiotics [83]. Altogether, 83% of CESIs resolved with PO ciprofloxacin, 17% required catheter removal, and 22% developed *Pseudomonas* infection several months after apparent resolution of CESI. These findings highlight both the resiliency of *Pseudomonas* and the importance of infection prevention.

Patients with prior infections are seemingly more prone to develop cuff infections in the future. Prophylactic antibiotics for 3 – 6 weeks after catheter placement, timely diagnosis and elimination of *S. aureus* nasal carrier states, effective use of non-soap and water catheter exit site care and avoidance of trauma are essential to decreasing CESIs. Sterile dressings for at least 6 weeks also tend to improve outcome. Mupirocin ointment applied at the exit site significantly lowered the incidences of *S. aureus* CESIs (86% decrease) and peritonitis (reductions of 69% for *S. aureus* peritonitis and 38% for all peritonitis),

as well as the catheter removal rate attributable to *S. aureus* infections [75]. The use of a silver ring did not appear to be effective in preventing exit site infections in a randomized, multicenter, clinical trial. Ultraviolet (UV) radiation may be helpful in eliminating bacteria as demonstrated in a small study (68 patients) in which 10/18 cases receiving UV radiation became culture-negative.

Chronic tunnel infections in children and adults may justify simultaneous removal and replacement of the CAPD catheter [89]. The catheter should be placed on the contralateral side with the internal cuff in the midline using the same entrance to the peritoneal cavity. Dialysis can be resumed immediately after the operation with low volumes. Only 4/23 pediatric patients in one clinical experience relapsed within 3 months, with the main causative agent being *S. aureus*. Automated PD can be started within one day of catheter placement and continued for 7 days with low volumes in patients who have previously been on CAPD. Utilizing this technique, patients in 38/40 procedures could successfully continue PD. Some surgeons may elect to create a new entrance on the contralateral side. Simultaneous removal and replacement should occur only if there is no evidence of active infection. Patients should receive 3 – 6 weeks of antibiotic prophylaxis. Further work in this area is needed to define the best approach.

S. aureus Nasal Carriage

The relationship between nasal carriage and risk of CESI and subsequent peritonitis is still controversial. The Danish Study Group of Peritonitis in Dialysis [117] and other studies reported that *S. aureus* infections occurred significantly more frequently among carriers in both HD and PD. In general, nasal carriage *S. aureus* is associated with risk of postoperative wound infection and of exit site infection in patients on chronic PD and intermittent HD. The Danish group found 59.5% of HD patients and 51.2% of CAPD were *S. aureus* carriers. Permanent carriage was usually primary nasal (44% HD, 34.9% CAPD), with rare skin carriage alone. Nasal carriage appears to be associated with a much higher rate of CESI. The incidence of infection was higher in diabetics (26.3% vs. 10.3% in non-diabetics), even though diabetics were not significantly more frequent carriers (60.5 vs. 55%). The higher infection rate despite similar carrier rates may suggest that diabetics are at higher risk for *S. aureus*, and need aggressive treatment. Luzar et al. noted that 45% of their patients and 77% of diabetic patients were nasal *S. aureus* carriers before catheter insertion [64]. CESI occurred in 0.4 episodes/patient-year in carriers and 0.1 episodes/patient-year in non-carriers. *S. aureus* carriage has also been found more often in patients with previous *S. aureus* peritonitis. Interestingly enough, one-half of spouses were carriers, with the same phage type and carrier state. Thus, the carrier state seems unrelated to age, gender, and presence of DM. Twenty-eight of 167 patients had MRSA nasal carriage in one study. The patient drop-out rate from infection for MRSA was comparable to pseudomonal and fungal infections, but significantly higher than methicillin-sensitive *S. aureus*.

CESI does not always result from nasal carriage, and most exit site infections occurred among patients without previous *S. aureus* colonization. And yet based upon a number of studies, eradicating *S. aureus* nasal carriage even in patients with one positive culture may decrease the risks for CESI and subsequent peritonitis. The quest for prophylaxis rather than treating individual episodes is spurred by the suboptimal current treatment of *S. aureus* with significant risk for relapse and catheter loss. Several studies have evalu-

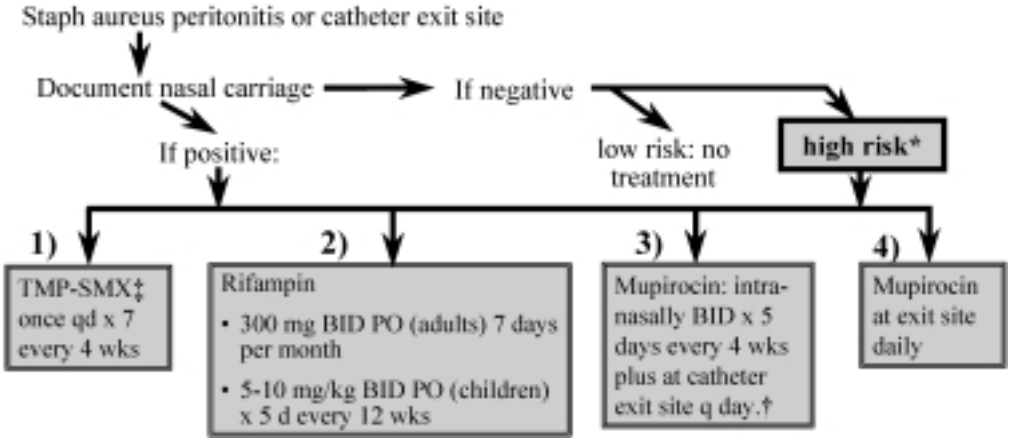


Figure 13. Prophylaxis for S. aureus: Initiate therapy (1, 2, 3, 4) for: culture positive (nasal carriage), *high risk patients** (> 65 years of age, diabetes, serum albumin < 3.0 mg/dL, second S. aureus infection) or if S. aureus rate > 40% of all CES infections; *low risk*, no therapy.
†Except in patients with polyurethane catheters. ‡TMP-SMX: trimethoprim-sulfamethoxazole.

ated varied prophylactic techniques to prevent the development of *S. aureus* CESIs in both children and adults (Figure 13). Certain strategies may increase the risk for complications (i.e. rifampin results in the development of resistance when given alone), and patients will likely need periodic retreatment or cycling with antibiotics to eradicate the carrier state. The greatest impact of prophylaxis with TMP-SMX was evident during the first 3 months of therapy. Local application of antibiotics at those areas most noted for colonization, i.e. naries and PD access port, resulted in only temporary bacterial elimination. Mupirocin, predominantly bacteriostatic in action, is bacteriocidal at the higher concentrations achieved following topical application, and was effective in terminating the normal carrier state in 65 – 100% of cases. Nasal mupirocin (calcium mupirocin 2%) administered twice daily for 5 consecutive days every 4 weeks was demonstrated in a large multicenter study to reduce the rate of exit site infection. Mupirocin calcium ointment 2% and cyclic oral rifampin 600 mg for 5 days every 3 months are equally effective in reducing *S. aureus* catheter infection, however many patients discontinue rifampin due to side effects. Even though resistance may occur with mupirocin, the selection of mupirocin-resistant clones is slow and stepwise. While application of mupirocin in MRSA may lead to increased resistance, particularly because of the presence of the MEC gene associated with multiple antibiotic resistance, applying the mupirocin ointment 3 times a week rather than daily may offer less risk for resistance.

Antibiotic Toxicity

Varied individual plasma clearances and risks of drug toxicity argue for obtaining drug levels for patients receiving vancomycin and/or aminoglycosides. Vestibular toxicity due to aminoglycosides in PD patients may be of more concern because of the relatively steady state serum levels believed to be more toxic than the high peak serum levels followed by very low trough levels seen with

intermittent dosing. Although some studies note no association between ototoxicity and serum aminoglycoside levels, others have shown that both high peak and high trough levels are correlated to ototoxicity. Approximately 12.5% of ototoxicity results from the use of aminoglycosides. In 46 dialysis patients, Antonelli et al. found that older patients had significantly longer auditory nerve and brain stem conduction times, indicating a subclinical disorder of the auditory nerve function which might increase risk for ototoxicity [5]. The current recommendation is to screen for high frequency auditory abnormalities and vestibular ocular reflex dysfunction in high-risk patients prior to aminoglycoside use, since the toxic effect of aminoglycosides is additive.

The toxic effect of vancomycin on the cochlea of CAPD patients is rare if serum levels are monitored closely. Tinnitus and high-tone hearing loss are recognized complications of vancomycin therapy and are frequent antecedents to deafness. Damage to the auditory nerve, initially affecting high-frequency hair cells, then middle- and low-frequency hair cells, is irreversible, although toxic changes may be delayed for weeks or months after exposure. Damage is determined more by the cumulative level rather than by the daily dose. Vancomycin administered in combination with an aminoglycoside may be synergistic in producing ototoxicity.

Quinolones, increasingly used for the treatment of infection, have several clinically significant drug interactions. Quinolones may inhibit the metabolism of certain drugs, and when given concomitantly with divalent or trivalent cations, the action and concentration are reduced. Quinolones increase serum theophylline and caffeine concentrations; and combination with warfarin raises the INR (the international anticoagulant marker). Magnesium sulfate/aluminum antacids, iron, enteral feedings, calcium (Ca) products and zinc decrease the absorption of quinolone, and should not be taken at the same time.

Cardiovascular Disease

Overview

The most common cause of death in ESRD is cardiovascular disease, accounting for nearly 50% of deaths in US patients. Cardiovascular complications that can occur in PD include myocardial structural abnormalities, valvular abnormalities, increased risk for arrhythmias, lipoprotein alterations, vascular disease, autonomic impairment, hypotension, hypertension, pericardial disease and modality-specific risk factors for vascular ischemia. To date no study has convincingly demonstrated that patients on CAPD are at greater or less risk of cardiovascular, peripheral-vascular or cardiovascular events when compared to individuals on HD. Bloembergen et al.'s analysis of data from the United States Renal Data System (USRDS) demonstrated that ESRD patients treated with PD had a 19% higher adjusted mortality risk than those treated with HD, with a third of the excess mortality stemming from myocardial infarction (MI) and cerebrovascular accidents (CVA) [10]. More recent analysis of these data by Vonesh et al. refuted this finding and demonstrated that the only cohort at potentially greater risk on PD was diabetic females over the age of 55 years [109]. Other studies have shown no difference or a higher risk in HD compared to PD. Port et al. examined possible factors that may have an impact on the observed outcome differences between PD and HD [87].

Myocardial Structural Complications

Both progression and regression of left ventricular hypertrophy (LVH) have been described in patients on PD. Differences in hydration, methodology, and hypertensive control could all be contributing factors. Progression of LVH has been correlated to increased blood pressure (BP) and cardiac index. Hypercirculation secondary to hypervolemia theoretically will negatively affect blood pressure control in PD especially in diabetic patients. Abnormal left ventricular filling, impaired aortic elasticity, increased peak systolic pressure, increased stroke work index, and higher cardiovascular systolic volume may all contribute to LVH in PD patients. Non-survivors are more likely to have lower left ventricular ejection fractions and higher cardiovascular systolic volumes (pump dysfunction) compared to survivors. One can also see impaired diastolic left ventricular function even without LVH, perhaps due to increased cytosolic Ca^{+} and ultrastructural changes characterized by cardiac fibrosis with interstitial proliferation and expansion. While LVH can develop in patients on PD, clinically there a significantly lower left ventricular end diastolic pressure, left ventricular end systolic volumes, stroke index and cardiac index, and a higher mean velocity of circumferential fiber shortening in PD compared to HD. These physiologic events may explain why LVH is present in approximately 52% of patients on CAPD, but 93% on HD [3].

The actual PD prescription may adversely affect cardiac function in certain patients. The higher the dialysate dwell volume in patients with LVH, the greater the alteration in left ventricular internal dimensions due to increased intra-abdominal pressure. Systolic function decreases in such individuals with infusion of 2.5 – 3 L volumes. This effect of intra-abdominal pressure on cardiac performance is especially important in PD patients with severe hypertrophic cardiomyopathy. These individuals may experience a decrease in cardiac preload if IP volumes > 2.5 L are instilled. Hypotension may result during the dwell phase when intra-abdominal pressure is highest, possibly reducing venous flow to the heart. In animal models a step-wise increase in intra-abdominal pressure results in a graded decrease in cardiac output. Findings in several dog experiments have demonstrated that intra-abdominal pressure > 20 mm Hg decreases cardiac output and causes a redistribution of regional blood flow. In most settings where UF rate is slow, there should be no significant effect on cardiac preload.

The two risk factors independently associated with the development of LVH are systolic hypertension and older age. When evaluating the impact of pressure on LV mass, Harnett et al. noted the mean systolic BP in the group who developed LVH was 150 ± 13 mm Hg, compared to 137 ± 16 mm Hg in controls [39]. BP is significantly lower on PD than on HD over time. Hajjar et al. [38] in a crossover study of 68 patients who changed dialysis modalities demonstrated a 16 mm Hg-increase in BP in patients moving from PD to HD and a 14 mm Hg decrease in patients moving from HD to PD.

Anemia also plays a role in increased LV dilatation and LV mass. Although left atrial chamber volume, and LV mass and chamber volume decrease with good BP control, structural abnormalities occur if hypertension is untreated when receiving erythropoeitin (EPO). While gender may affect certain mediators of LVH in dialysis patients, little is known about the impact of PD vs. HD on these factors. Previous reports demonstrated that both baseline LV mass and cavity volume were strong predictors of late mortality in patients with uremia. Both LV dilatation with normal systolic and high cavity volume (>

120 mL/m^2) and low mass-to-volume ratio (> 1.8 mL/m^2) were independently associated with late mortality in uremia. Daily dialysis with PD may optimize structural modeling as compared to intermittent therapy with HD. LVH may be a frequent finding in children on dialysis. PD may offer a lower risk of development of LVH, especially in younger children.

Interestingly, protein-calorie malnutrition (loss of approximately 40% of initial body weight) has been proven to adversely affect the heart. In animal experiments loss of subcutaneous fat stores, reduction of myocardial glycogen content, myocardial atrophy and interstitial edema (increased myocardial water content, along with the formation of intracardiac edema) from malnutrition may compromise cardiac function and survival. These findings can occur in patients with cardiomyopathy on PD who suffer from continued cardiac cachexia despite aggressive PD regimens. Dialysis alone may not reverse the sequelae of end-stage heart failure.

Valvular Abnormalities

Sclerosis or calcification of the mitral valve or annulus is associated with decreased survival in PD patients. This may be related to a high calcium-phosphorus (Ca × P) product or the use of standard Ca rather than low Ca dialysate over long periods of time. Historically, mitral calcification was favored by longstanding pre-dialysis arterial hypertension, and by a high Ca × P product during PD. Decreased survival with mitral calcification results from decreased systolic left ventricular function or severe valvular incompetence. There is now a well-documented correlation between serum Ca, a high Ca × P product, and the risk of calcified aortic stenosis. Therefore, inadequate Ca control in PD might add to the already existent cardiac risk seen in ESRD.

Arrhythmias

Arrhythmias are frequent among the dialysis population [103]. Twenty-four percent of patients demonstrate > 10 ventricular ectopic beats/hour, with 11% noticing episodic atrial fibrillation, and 8% ventricular tachycardia. Heart block occurs in < 2%. Overall, 51% of patients demonstrate arrhythmias on Holter monitoring. On autonomic testing, 61% had abnormal heart rate responses, while 63% had abnormal BP responses. These changes support a causal relationship between arrhythmias and autonomic neuropathy, which is exacerbated by dialysis. Canziani et al. noted a significantly decreased incidence of mild and severe arrhythmias in PD compared to HD patients [14]. Factors which may be linked to ventricular arrhythmias on PD are age, LV mass index, and an abnormal LV wall score.

Ventricular tachycardia, ventricular fibrillation, torsades de pointes and long QT syndrome have been reported in patients taking Cisapride alone or in combination with a number of other medications (e.g. erythromycin, clarithromycin, fluconazole, and ketoconazole) that inhibit cytochrome P4503A4. Cisapride should not be used in PD patients with a prolonged QT interval at baseline, those with a history of torsades de pointes or those with long QT syndrome. It should also be avoided in patients with sinus node dysfunction and in those with second or third degree atrioventricular block.

Atherosclerosis and Hyperlipidemia

Because cardiovascular disease continues to be the main risk for death in patients on dialysis, many reports have been published in the past decade on modality-specific lipoprotein differences (total levels, clearance rate,

receptor modification, particle size, transport). CAPD increases total cholesterol, triglyceride, total cholesterol to HDL ratio, and apolipoprotein-B to apolipoprotein-A (apoA/apoB) ratio [100, 114]. The overall clearance of LDL is markedly less in CAPD vs. HD, with a fractional catabolic rate for LDL of 0.268 ± 0.072 pools/day in PD vs. 0.376 ± 0.045 in HD [45]. This may be due to alterations in LDL structure or the LDL receptor itself. Decreased binding may be attributed to an increase in advanced glycosylation end products or a chemical modification due to uremia itself. The apoB/apoA ratio is significantly higher in diabetic vs. non-diabetic ESRD patients. Furthermore, the dialysis modality may alter distribution of the LDL particle size, possibly as important a risk factor for atherogenesis as absolute LDL levels. In a study of 65 ESRD patients, 48% of the CAPD patients had small LDL particle size vs. 23% for HD patients [82]. Lipoprotein clearances correlate with molecular mass, plasma concentration and dwell times, with a preferential clearance of HDL in PD amounting to approximately one-third of the daily synthetic rate. The mean daily clearance of $apoA_1$, a major HDL protein, is twice that of apoB, which is the predominant protein associated with LDL.

Lipoprotein A (Lp(a)) may be a genetic marker for increased coronary artery disease (CAD) risk in both dialysis and nondialysis patient cohorts, and may vary by country and ethnic or racial group. Lp(a) values are clearly affected by the mode of the renal replacement therapy, being highest in CAPD. The vascular significance of Lp(a) may depend not only on the actual level but also on the presence of procoagulant factors [58]. Patients with CAD had higher fibrinogen concentrations (628 ± 59 mg/dL) and higher Lp(a) concentrations (43.5 mg/dL). Petersen et al. examined anticardiolipin antibodies and Lp(a) levels in 22 PD and 64 HD patients [85]. The mean Lp(a) level on PD was 56.7 mg/dL and 38.8mg/dl on HD (NS). All patients who suffered an MI or CVA had Lp(a) levels > 30 mg/dL.

Patients with increased peritoneal membrane transport characteristics demonstrate a more atherogenic lipid profile. Heimburger et al. demonstrated that the increased Lp(a) in CAPD was related to the peritoneal glucose absorption, and peritoneal membrane type [40]. The importance of carbamylation and glycosylation on lipoprotein atherogenicity in CAPD is undetermined. The presence and concentration of advanced glycosylation end (AGE) products may increase the risk for atherosclerosis in PD. AGE-modified LDL levels may represent a particularly atherogenic form of LDL. AGE-LDL as well as AGE peptides are likely to contribute to the development of atherosclerosis in diabetic patients. There is a strong correlation between serum total cholesterol and the AGE-LDL (AGE apoB and AGE-lipid). The development of new dialysate solutions may ameliorate lipoprotein abnormalities in ESRD patients, since a positive correlation appears to exist between glucose absorption from the dialysate and Lp(a) values. Also hypoalbuminemia, especially in the high-transport group, appears to be an important trigger for the elevation of Lp(a) in CAPD. Seemingly, this may be a modifiable risk factor. Lp(a) is significantly decreased by regular infusions of albumin. Yet, a 6-month prospective crossover study evaluating the effect of one postprandial 1.1% amino acid dialysate demonstrated no effect on dyslipidemia in CAPD patients [73].

Red blood cell (RBC) transport may also play a role in the lipoprotein abnormalities observed in PD. The decreased transfer of cholesterol between RBCs and the antiatherogenic HDL fraction may hinder transport from peripheral tissues and result in increased

atherosclerosis risk. In ESRD patients on dialysis, low levels of plasma HDL-3 cholesterol levels, HDL-3 phospholipid content and net transport of RBC cholesterol-2-isolated HDL were significantly lower compared to controls.

A number of reports have examined whether the dialysis technique itself changes lipid profiles in long-term CAPD patients. In a group of 16 stable nondiabetic PD patients with initial total cholesterol < 230 mg/dL, total cholesterol triglyceride HDL, LDL, and apoB/apoA_1 did not show significant changes by serial measurements from 6 – 13 months following initiation of PD [53]. There was no relationship to Lp(a) levels and time on CAPD.

Aortic pulse wave velocity (A_0PWV) and aortic calcification were also examined in CAPD patients to try to estimate risk of accelerated atherosclerosis. While lipid values did not denote patients with progressive vascular disease, A_0PWV increased in 46% of patients. The degree of abdominal aortic calcification was divided into two separate categories, with the greatest calcification seen in patients on CAPD > 5 years. It is unclear whether these findings are modality-specific or related to uremia since HD patients were not prospectively examined.

A meta-analysis comparing the efficacy of various antilipidemic therapy for PD, HD and transplant patients demonstrated the effectiveness of β-hydroxyl-β-methyl glutaryl Cofactor A (HMG-CoA) reductase inhibitors in lowering abnormal lipid patterns. A number of medications are effective in treating dyslipidemias in CAPD as described by Massy and Lye [65, 67]. Both statins and fibric acid derivatives have proven effective, although individual differences mandate monitoring of lipid levels. Target treatment lipoprotein levels may need to be further decreased to control vascular atherosclerosis in dialysis patients. Both Nevalainen and Lahtela reported that IP insulin, while achieving better glycemic control in PD and improved insulin sensitivities as compared to subcutaneous (SC) administration, results in increased serum triglycerides and total cholesterol and decreased HDL cholesterol – possibly due to a direct effect of IP insulin on the liver [60, 77].

While the levels of Lp(a), total cholesterol, and LDL may increase in CAPD, the lipoprotein patterns from CAPD patients may exhibit a resistance to in vitro oxidation, a possible step in the development of atherosclerosis. Podrez et al. noted that Lp(a), but not LDL, is oxidized in plasma of CAPD patients [266]. It is unclear whether Lp(a) is more prone to oxidation than LDL. Another possibility is that Lp(a) is preferentially oxidized in renal failure patients due to its lower plasma clearance as compared to LDL. Since Lp(a) binds better to epithelial cells and platelets than LDL, it is possible that such binding can facilitate Lp(a) oxidation in vivo.

A retrospective review of 53 pediatric PD patients likewise showed a high incidence of hypoalbuminemia, hypertriglyceridemia, hypercholesterolemia, and associated low levels of HDL unchanged while on PD [95]. As with adult PD patients, their risk for future atherosclerosis may rest with not just the lipoprotein levels, but rates of oxidation and effects of newer nonglucose dialytic solutions.

Abnormal Vascular Pro-ischemic Factors

The risk for thrombosis, from both vascular calcification and loss of autoregulation leading to altered flow, could increase ischemic events. Key components of the fibrinolytic system are tissue plasminogen activator

(TPA) and the fast-acting inhibitor of TPA plasminogen activator inhibitor (PAI). In uremic patients, lipoprotein abnormalities and derangement of the fibrinolytic system with increased PAI levels may contribute to the development of atherosclerosis obliterans (ASO) or cardiovascular disease (CVD). TPA and PAI are synthesized and secreted by vascular endothelial cells. Thus, in damaged vessels there would be a slow, continuous release of TPA and PAI. Plasma fibrinogen, PAI activity, and factor C are significantly elevated in CAPD patients, while TPA is increased in both HD and PD. These data raise concerns regarding the risk for increased thrombosis on PD vs. HD [18]. This risk might be modified by the use of less hyperosmotic dialysate, optimization of albumin levels, control of hypertension, and treatment of lipoprotein values with HMG-CoA reductase inhibitors. A comparison of CAPD patients with and without ASO with controls [56] showed significantly depressed serum albumin and HDL concentrations on CAPD, with a markedly elevated ratio of total cholesterol to HDL. CAPD patients with atherosclerosis had higher fibrinogen, total PA and PAI levels vs. normal and CAPD patients without atherosclerosis. TPA level was an independent predictor in a stepwise fashion for ASO. Serum albumin was inversely correlated to fibrinogen; however, no relationship to TPA and PAI was detected. There was no significant difference in certain lipids, lipoprotein and apolipoprotein values in male diabetic patients on CAPD. Female PD patients' levels of triglyceride apolipoprotein, apoB, low density lipoprotein (LDL), and cholesterol/HDL ratio were all significantly higher than those in normal females. Plasma levels of fibrinogen and von Willebrand factor (vWF), but not PAI, were higher both in the male and female compared to controls. The hypoalbuminemia in many dialysis patients may account for an increase in fibrinogen synthesis.

Ecosaenoid precursor (arachnidonic acid and ecosapentanoic acid) levels have been evaluated in CAPD patients with and without DM. Arachnidonic acid levels were significantly higher, while eicosapentaenoic acid (EPA) levels were significantly depressed in CAPD patients [43]. The lowest EPA values are found in Type I (insulin-dependent) DM CAPD patients. The combination of increased arachnidonic acid, lack of N-3 fatty acids, and reduced prostaglandin-12 biosynthesis lead to a higher formation rate of thromboxane A2, which may promote atherogenesis via vasoconstriction and platelet aggregation. Therefore, in addition to the typical dyslipidemias found in CAPD patients, high levels of Lp(a) and fibrinogen may contribute to the elevated risk of CAD and other cardiac complications.

Hyperhomocysteinemia is a well-established, independent risk factor for atherosclerosis, and thromboembolic and vascular disease, especially in ESRD. Hyperhomocysteinemia (> 16 μmol/L) is observed in PD, while homocysteinemia is more intense (29.8 μmol vs. 19.9 μmol) and prevalent (90.8% vs. 67.4%) in HD as compared to PD patients [81]. Diabetic PD patients should be screened and aggressively treated with high folic acid doses when elevated levels of homocysteine are detected.

Vascular Disease Patterns

Vascular disease in CAPD patients is a major cause of death. Arterial calcifications, composed primarily of Ca salts found chiefly in the internal elastic lamina of the intima and in the media of the arterial walls, generally tend to progress in patients with ESRD. Whether arterial calcifications occur during dialysis due to the procedure, or just to the

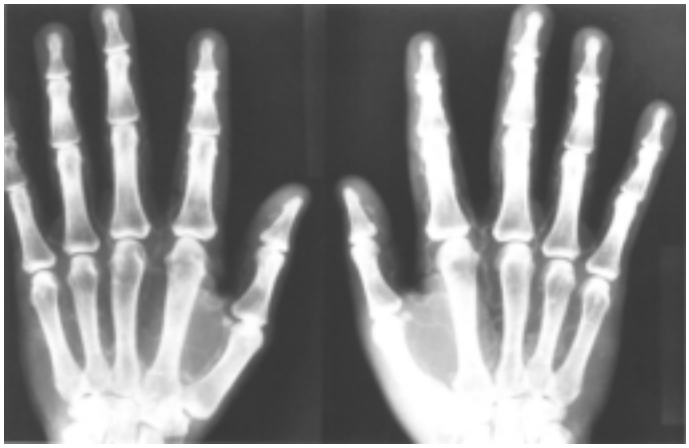


Figure 14. Peripheral (digital artery) vascular calcifications can occur in patients on PD, as demonstrated in this 42-year-old female on PD for six years.

greater prolongation of life in the presence of chronic renal failure is unclear, although on average, vascular calcification starts approximately 9 years after onset of ESRD. Peripheral vascular calcifications, once established, may progress on both HD and PD. Lipid deposition, intimal hyperplasia, and thrombosis cause vascular damage, with endothelial damage mediated via smooth muscle cell migration and proliferation, secretion and synthesis of extracellular matrix (e.g. collagen, glycosal-aminoglycan, glycoprotein, and elastin), and platelet disruption with thrombosis. Deep vessel wall injury associated with reduced fibrinolytic activity and increased PAI activity may lead to intravascular thrombosis and impaired thrombus resolution. Two primary patterns of vascular calcification occur: axial (aortic and iliac in femoral vessels), and peripheral (digital arteries) (Figure 14). Most patients have evidence of both types while on dialysis. Furthermore, the presence of these vascular calcifications decreases vessel compliance and may reduce autoregulation distal to a stenosis in the coronary bed. In prior studies age, systolic BP, hyperparathyroidism, plasma phosphorus (P), and vitamin D were principal determinants of severity in the rate of progression of vascular calcifications.

Rheologic factors (blood flow, vessel radius, pressure gradient, and blood viscosity) may contribute to atherogenesis, thrombosis and ischemia both centrally and peripherally. Atherosclerotic patients have statistically significant increases in blood plasma viscosity compared to normal controls. Therefore, in a calcified vessel with both an inability to autoregulate and high plasma viscosity, thrombosis may occur in the presence of increased procoagulant concentrations. In the setting of endovascular injury from blood pressure and hyperlipidemia, thrombosis may lead to obstruction, lack of distal autoregulation, and tissue infarction.

A large proportion of patients reported with progressive vascular calcifications have DM, and all of the diabetics in the study by Meema et al. developed calcifications [70]. The same study demonstrated no differences in serum Ca and P, Ca × P product, parathyroid hormone (PTH), and alkaline phosphatase levels. Other studies have shown a correlation between serum Ca or the Ca × P product and the risk of calcified aortic stenosis. Increased arterial stiffness and cardiac overload were linked to severe coronary arterial calcifications and an increase in arterial pulse wave velocity.

Vascular calcifications may contribute to decreases in distal blood supply and, combined with peripheral sensory and autonomic neuropathy, may affect oxygen and nutrient delivery to tissues causing ischemia, ulceration, infection, and need for amputation. More than 69,000 major lower extremity amputations for ischemia were performed in the US in 1989 [25]. The higher the amputation rate, the higher the mortality rate. The incidence of lower extremity amputations among patients on HD was estimated to be 2.9% for unilateral amputations and 1% for bilateral amputations. Few data exist for PD cohorts. ESRD has a serious adverse impact on hospital mortality and long-term survival rates after amputation. The most common causes of death following amputation are cardiac events. ESRD patients were more likely to have CAD than non-ESRD patients (78 vs. 42%). The prophylactic value of hygiene of ischemic lower extremities is illustrated by a 3-fold decrease in amputation rates in patients with diabetes who participated in a foot education program.

Stroke is the third leading cause of death in the general population, with an even greater risk in the ESRD population. The risk of death for stroke may actually be greater for patients on PD vs. HD despite a lower prevalence of preexisting cerebrovascular disease and better control of BP, according to USRDS data [68]. The risk for death from stroke on PD compared to HD was nearly 2-fold greater for elderly, diabetic, African-American, and female patients. It is not clear whether this difference might reflect established cerebrovascular disease at dialysis initiation or an actual dialysis modality effect. Moreover, stroke mortality itself is related to factors such as inadequate dialysis, uncontrolled hypertension, and hypervolemia. Therefore a major issue is whether the modality itself or its prescribed use affects the death rate from stroke in ESRD patients. Considering the risk for progressive atherosclerosis in ESRD, identification of high-risk patients and aggressive treatment are indicated.

Avoiding coronary artery events is extremely critical especially in diabetic patients on PD. The FINMONICA myocardial infarction registry study [72] demonstrated that in 3442 patients, 45% of all diabetic men and 38.8% of all diabetic women with their first MI died within one year. These figures contrasted with 32.5% for nondiabetic males, and 22.1% for nondiabetic females. A substantial portion (28% of the males and 10% of the females) of these deaths occurred outside the hospital. Aggressive treatment with antilipidemic drugs, identification of patients with procoagulant risk, and intervention for critical lesions amenable to angioplasty and stenting, and/or cardiac revascularization should be implemented.

A major difference in death rate from myocardial ischemia and infarction exists between the United Kingdom and Italy in both the overall renal replacement therapy and the HD group [61, 92]. In males on PD, the disparity between countries is more subtle. For both primary renal diseases and diabetic nephropathy, the EDTA registry data for PD and HD demonstrated relatively lower cardiovascular mortality in the PD compared to HD patients; however, the relative cardiovascular mortality remains constant by modality over the last decade. Identifiable predictors of progression include: DM (accelerated, significant stenosis); interval between MIs; angina severity; chest pain with exercise; test endpoint; location of lesion in proximal right coronary artery (RCA), mid RCA, or mid left anterior descending artery (LAD); and stenosis morphology (single vs. tubular). Diabetic lesions tend to be more tubular than single, with disease localized to the RCA and LAD. Because of diabetic PD or HD patients'

increased risk for CAD, they should undergo regularly scheduled screening.

Hypotension

The prevalence of hypotension in CAPD patients varies in different populations from 10 – 15%, with hypovolemia causing 25% of these cases [1]. A study from the Toronto Hospital noted approximately 12% of the CAPD population developed hypotension. Twenty-five percent of the patients had hypovolemia as the etiology, 23% heart failure, 18% antihypertensive medications, and 34% unknown etiology. The mortality rate was higher among hypotensive patients than among nonhypotensive patients on PD. Physiologic night-time declines of BP ("dipping") were more significant and pronounced in PD than in HD. Those that appear most susceptible to hypotension are patients with demonstrated autonomic neuropathy, LVH, diastolic dysfunction, inappropriate activation of cardiac reflexes and abnormal vascular response.

Cardiovascular autonomic impairment can affect the peripheral circulation as well as the heart in dialysis patients and this may have implications for cardiovascular homeostasis. A comparison of peripheral blood flow responses and sympathetic vasoconstrictive reflexes in CAPD patients with matched control subjects has been previously reported [47]. Cardiac autonomic function assessed by standard tests of heart rate variability (deep breathing, Valsalva maneuvers and standing from a lying position) was significantly impaired in patients on PD compared to controls.

The QT_C interval may be used in the evaluation of autonomic neuropathy as a marker of venous tone reactivity. The main defects leading to hypotension are decrease in venous tone or increase in venous pooling of blood, decrease in overall venous return, and thus cardiac output. Proamitine (mitodrine hydrochloride) may help some cases of hypotension by acting selectively on venous and arterial α_1-adrenergic receptors without stimulating cardiac β-adrenergic receptors, thereby increasing venous tone and decreasing venous capacitance.

Cardiomyopathy secondary to right ventricular failure, ischemia, transplantation and its sequelae, viral infections, and infiltrative amyloidosis can also result in hypotension. Increasing numbers of cardiomyopathy patients with renal dysfunction and diuretic resistance are now starting PD for daily volume removal and the lower levels of hemodynamic stress on PD vs. HD. Anticoagulation may be needed to avoid thrombotic cerebrovascular complications, given the low flow, depressed cardiac output, persistent hypotension, and potential for arrhythmias in these patients. Cardiomyopathy secondary to amyloidosis is a contraindication to the use of digoxin, and calcium channel and beta-blockers.

Patients on PD may have a risk for uremic pericarditis due to inadequate dialysis (poor prescription design). Infective pericarditis documented by technetium^{99} scan following peritonitis has been reported.

Musculoskeletal Complications

Hypocalcemia, Hypercalcemia, and Hyperphosphatemia

Significant interest has been generated by the effects of varied dialysate Ca concentrations on serum Ca and PTH levels, renal bone disease management, and regulation of phosphorous (P) levels with medication on PD.

Hyper- and hypocalcemia are complications commonly observed in patients on PD. Ca mass transfer in PD depends on dialysate Ca concentration, ionized serum Ca, and the UF rate [115]. Fifty percent of patients with persistent hypercalcemia and hyperphosphatemia who were changed to low Ca dialysate achieved significant decreases in both Ca × P product and percent hyperphosphatemia. Ca balance is positive if dialysate Ca is ≥ 2 mEq/L. One and one-half percent dialysate results in an approximately 9.8 mg Ca uptake, whereas 4.25% led to a loss of 21 mg. Standard peritoneal dialysate has a relatively high Ca concentration of 3.5 mEq/L, which may result in hypercalcemia [113]. A number of studies have stressed the effect of different dialysate Ca concentrations on Ca fluxes in PD. Bro et al. showed that plasma PTH levels could be adequately controlled during a one-year follow up using 1.35 and 1.25 (but not 1.75) mM/L Ca dialysate concentrations without either hypercalcemia or the use of aluminum-containing phosphate binders [11]. In a 6-month multicenter study of 103 patients, total Ca was significantly lower (9.6 vs. 10.8 mEq/L), immunoreactive calcium (i-Ca) was depressed (4.76 vs. 5.15 mg/dL), and there were fewer episodes of hypercalcemia in patients using low Ca dialysate. Chagnac et al. found a 71% increase in Ca values when the dialysate Ca was further reduced from 1.25 to 1.0 mEq/L [19]. The decrease in dialysate Ca did not prevent the observed increased serum Ca, suggesting that lowering the serum PTH value reduces the ability of the bone to handle a Ca load within a few weeks. For severe hypercalcemia (serum Ca > 13 mg/dL), hospital pharmacies may need to prepare 0 mg/dL-Ca dialysate.

Kurz et al. [59] assessed the effect of differing dialysis modalities on Ca turnover in 57 HD and 38 CAPD utilizing tracer kinetic studies with ^{45}Ca orally and ^{47}Ca intravenously. Elevated PTH levels were found in 91% of all patients, whether on PD or HD. Serum concentrations of 25-hydroxycholecalciferol and alkaline phosphatase were markedly lower in CAPD than HD, and CAPD patients were less responsive to the action of immunoreactive PTH. A randomized, multicenter, controlled trial with 103 stable CAPD patients compared low-Ca (1.0 mM/L) vs. higher-Ca (1.75 mM/L) dialysate. All patients received oral Ca carbonate and calcitriol, and those with increased Ca were treated with aluminum hydroxide. Patients treated with low-Ca dialysate showed a 3-fold decrease in the incidence of hypercalcemia, with PTH levels > 2 times normal in 40% of cases.

Technetium^{99m} etidronate bone scan alterations progressed with time on dialysis especially in younger patients and those with higher intact PTH levels. Aggressive early treatment with optimal control of PTH is essential to avoiding bone disease with chronic renal failure (CRF), and for patients just starting PD. Maintianing a lower Ca will permit the administration of more Ca carbonate to control phosphate. This may be less of a problem with development of Renagel (sevelamer hydrochloride) which is a polymeric oral phosphate binder.

Hypocalcemia can occur in PD and is related to decreased oral intake, low vitamin D levels, dialysate Ca mismatch or after parathyroidectomy postoperatively. Decreased oral intake of Ca may lead to profound hypocalcemia and or tetany on PD.

Using standard CAPD volumes, approximately 10 mM of phosphate are removed per day with 2-L, or 15 mM/day if using 3-L volumes. Only high volume CAPD can cause a negative phosphate balance over a one-week period. Hyperphosphatemia can occur in PD and is primarily related to dietary intake of P, and noncompliance in taking P binders. While hypophosphatemia can occur on PD, it is un-

common. The main causes are refeeding in malnourished PD patients, overzealous phosphorous binder administration, inadequate intake, and secretory diarrhea.

Low-turnover Bone Disease (Adynamic Bone Disease)

Advanced renal failure may lead to either a high bone turnover (osteitis fibrosa) or low bone turnover. Three different groups of low-turnover bone disease occur in ESRD patients on dialysis: osteomalacia, aluminum-related, and adynamic lesions. In PD, osteomalacia is uncommon due to supplemental vitamin D. Low-turnover aluminum bone disease is also on the decline due to the use of nonaluminum-containing phosphate binders. Adynamic bone disease is characterized by low bone turnover, normal or low osteoid volume, and decreased bone formation rate, resulting in increasing numbers of microfractures and increasing the risk for clinically-apparent fractures. The diagnosis of adynamic bone disease is supported by normal or low PTH, unremarkable aluminum levels, higher ionized Ca, lower alkaline phosphatase, and a higher incidence of calcifications. The vascular calcifications seen with adynamic bone disease in PD patients may be secondary to hypercalcemia from lower skeletal Ca retention and lower plasma Ca efflux due to older age. Significant hypercalcemia and metabolic encephalopathy can occur especially in diabetic patients on PD and may not respond to a reduction of Ca in the dialysate. In this setting a bone biopsy should be performed to rule out a high turnover condition [31]. Unfortunately, the use of PTH levels did not predict the degree of bone turnover in half of the CAPD patients with values between 65 – 450 pg/mL. Low-turnover bone disease without aluminum toxicity is associated with secondary hyperparathyroidism, DM, hyperphosphatemia, hypocalcemia, altered vitamin D synthesis, impairment in PTH secretion and metabolism, and possible down-regulation of the renal PTH/PTHrP messenger RNA receptor. Moreover osteoblast type I collagen messenger RNA (mRNA) expression is lower in cells from adynamic bone vs. bone from hyperparathyroid states.

Adynamic bone lesions accounted for 50% of bone lesions seen in 268 dialysis patients described by Sherrard, and is more common in PD vs. HD (61% vs. 36%) [99]. Hutchinson et al. reported histologic abnormalities more commonly in older patients with a longer duration of dialysis (10 vs. 7.1 years), although 28% of patients had the lesion at the start of dialysis [46]. In an additional study, 31% of CAPD patients demonstrated adynamic or aplastic disease at the outset of treatment or within 12 months of starting PD. The management of adynamic bone disease should be directed to stimulating PTH to values 2 times normal.

Moderate hyperparathyroidism with intact PTH from 150 – 903 pg/mL can be effectively treated using 0.5 mg to 1.5 mg calcitriol twice weekly. Ca levels should be monitored and hypercalcemia treated by a transient reduction in dialysate or oral Ca intake. Vitamin D should be stopped for Ca levels > 11.5 mg/dL or 2.9 mM/L. Pulse therapy is contraindicated with the serum P > 6 mg/dL or 1.9 mM/L, with a plasma PTH < 120 pg/mL. In pediatric patients the use of high-dose pulse IV, IP or PO calcitriol therapies significantly decreases the serum PTH levels and retards the formation of osteitis fibrosis. Calcitriol decreases the synthesis and secretion of PTH by a direct effect on PTH gene transcription, as well as suppressing PTH by increased intestinal Ca absorption. Oral and IV bolus pulse calcitriol therapy are equally effective in suppressing PTH. Hyperphosphatemia can be aggravated

by suppression of PTH in some cases. A new drug, $^{19}nor_1$alpha-25 dihydroxy vitamin D_2, can suppress immunoreactive PTH levels, but does not have as great an effect on serum Ca and P levels. This difference in effect may be linked to a smaller affinity for the vitamin D receptors with less mobilization of Ca from the bone than calcitriol, and less affinity for vitamin D binding protein. Treatment of hyperparathyroidism must be carefully balanced, as it may lead to the development of adynamic bone lesions with oversuppression of PTH and increased Ca intake or hypercalcemia in certain cases.

The vast majority of patients on chronic dialysis demonstrate histologic evidence of osteodystrophy. The long-term implications of this are unknown.

Dialysis-related Amyloidosis

The dialysis-related amyloidosis characterized by β-2 microglobulin amyloid deposition appears not to be a consequence of dialysis treatment alone, but rather a complication of CRF initially recognized in patients receiving long-term HD. This consequence can also occur in PD but the small number of patients on PD for > 10 years limits the risk [17]. The histologic prevalence of musculoskeletal β-2 microglobulin amyloid deposition increases with duration of dialysis from around 20% at 2 years for HD, to 100% after 13 years, although β-2 microglobulin amyloidosis can be seen in patients who have not started therapy.

β-2 microglobulin's high affinity for collagen explains the predominance of joint and bone disease. β-2 microglobulin amyloidosis deposits are preferentially deposited in bone, articular cartilage, synovium, and ligaments. Only the number of bone lesions is significantly correlated with patient age and negatively correlated with residual renal function. Patients characteristically present with a triad of symptoms with shoulder pain (scapulohumeral periarthritis), carpal tunnel syndrome, and flexor tendon deposits in the hands. The diagnosis can be made from X-ray, ultrasonography and/or scintigraphy with radiolabelled β-2 microglobulin scanning using radiolabelled serum amyloid P. Hand lesions are found in 85% of patients with dialysis-related amyloidosis. Synovial thickening may be shown on sonography and positive scintigraphic imaging delineates the presence of dialysis-related amyloid. A rotator cuff thickness > 8 mm and echogenic pads between muscle groups of the rotator cuff are strongly suggestive of β-2 microglobulin. The presence of at least one of these two findings in ultrasonography of the shoulder provides a relatively sensitive and highly specific noninvasive adjunct to the clinical diagnosis of β-2 microglobulin amyloidosis in the patient undergoing long-term dialysis. However, identification of β-2 amyloid by Congo red staining of biopsy specimens, or centrifuge synovial fluid sediments remains the gold standard for diagnosis.

The pathogenesis of β-2 microglobulin amyloidosis is incompletely understood. Several important contributing factors include levels of β-2 microglobulin, limited proteolytic cleavage of β-2 microglobulin, modification of β-2 microglobulin and other proteins with AGE, and elevated circulating levels of proinflammatory cytokines. Only renal transplantation may slow or halt the progression of β-2 microglobulin amyloidosis. PD and HD do not appear to arrest its development. Preservation of residual renal function early on in PD may be helpful in avoiding accumulations of β-2 microglobulin, and may have a long-term impact in avoiding this condition once patient has been transferred to HD. It is unclear whether the incidence, prevalence and rate of progression of β-2 mi-

croglobulinemia differ according to dialysis modality. It is essential that amyloidosis be prevented by removing the β-2 microglobulin by dialysis, to counterbalance the β-2 microglobulin amyloid generation. In comparing HD, hemofiltration or CAPD, metabolic studies with radiolabelled β-2 microglobulin indicated a slight increase in β-2 microglobulin synthetic rate in uremic patients irrespective of dialysis technique (4.49 ± 2.60 vs. 2.68 ± 1.3 mg/kg/day) [78]. More recent pharmacologic agents, e.g. antiamyloid fibril (anthracyclin-4-iodo-4-deoxydoxoribirin) may help in amyloid load reduction.

Erosive Azotemic Arthropathy

Another uncommon bone lesion that may occur on PD is erosive azotemic osteoarthropathy (EAO). EAO typically occurs in the distal interphalangeal joints of the hands, and has a higher prevalence in HD vs. PD (19% vs. 6%). Affected patients tend to be older with a history of carpal tunnel syndrome. EAO is not related to severe secondary hyperparathyroidism.

Dialysis patients are at risk for a low bone mineral density (BMD) osteopenia as a consequence of hyperparathyroidism, acidosis, secondary amenorrhea, chronic hepatitis, and aluminum exposure. Dual energy X-ray measurements of BMD showed significantly higher values in PD vs. HD (0.985 vs. 0.94 g/cm^2). BMD may increase with time on dialysis. While still abnormal, CAPD patients have better bone mineral metabolism than HD patients. Little has been written regarding BMD osteopenia in the PD population, however there does not appear to be an increase in osteopenia in patients on PD.

Diabetic PD patients are at greater risk for aluminum deposition compared to nondiabetic patients. Even small amounts of aluminum-containing phosphate binders can increase the risk for aluminum deposition on bone surface compared to nondiabetics. Therefore it is essential to avoid all aluminum-containing binders in diabetic patients with hyperphosphatemia.

Carpal Tunnel Syndrome

Carpal tunnel syndrome occurs in 14% of patients on PD. Nomoto et al. examined records from 5050 patients undergoing PD in Japan between 1980 and 1993 [79]. Only 7 developed carpal tunnel syndrome. All 7 were females. Two to 31% of patients on HD are afflicted with carpal tunnel syndrome. Benz found 18% in a 5 – 97-month follow up of CAPD patients [8]. Apparently CAPD minimizes the emergence of carpal tunnel syndrome with its characteristic pain, numbness, and tingling in the hands. Amyloid could be a causative factor in CAPD carpal tunnel syndrome. However, β-2 microglobulin levels were markedly lower in CAPD vs. HD patients, and yet, they were greater than those seen in normal patients. This may be directly related to preservation of residual renal function on PD and more optimal middle molecule clearance.

Myopathy/Calcifications

PD patients may develop muscle weakness, decreased endurance and easy fatigue. While the etiology is complex, both vitamin D and carnitine deficiencies have been implicated. Vitamin D deficiency is one of the causes of uremic myopathy in PD. Although vitamin D administration causes symptomatic relief, electromyography (EMG) abnormalities (polyphasic motor nerve unit potentials of brief duration and decreased amplitude and

fibrillation potentials) may not significantly change. The effectiveness of proponyl, used to improve strength, is open to debate.

Carotene deficiency has also been linked to myopathy in PD patients. While carotene deficiency can result in defective oxidative ATP synthesis, there is little evidence to suggest that skeletal muscle metabolism is affected by PD. Patients with anemia and those patients engaging in anaerobic exercise do not respond clinically to propionyl-L carotene supplementation [105]. Moreover, oxidative metabolism did not normalize with carotene administration, suggesting anemia and carotene deficiency are not the only causes of mitochondrial dysfunction leading to myopathy in PD.

Extraskeletal calcifications (Figure 15) have been associated with an increase in Ca-P product, excess PTH, and extracellular fluid in PD patients. Two main types of extracellular calcifications can occur: visceral and periarticular. There is an association between large soft tissue Ca deposits and aluminum intoxication. Metastatic calcifications, sometimes multiple, can be detected by bone scintigraphy technetium^{99m} methyldiphosphonate (MDP). Several reports have demonstrated a beneficial effect of diphosphonate (disodium ethan-1-hydroxy, 1-diphosphorates) on reduction of tumoral calcinosis in PD and HD.

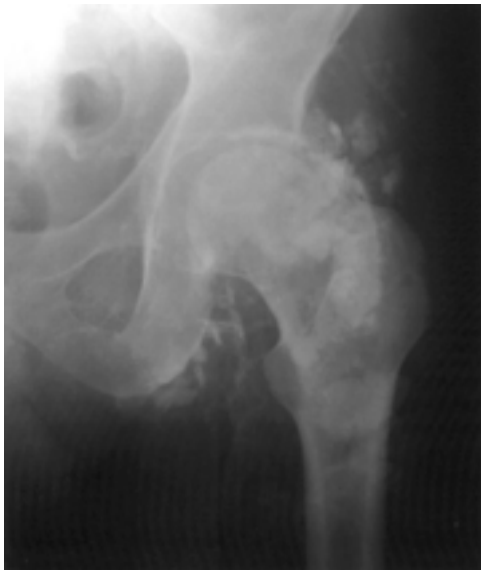


Figure 15. Periarticular extraskeletal calcifications can occur in patients on PD associated with an increase in calcium P product and excess PTH. Patients may demonstrate significant symptomatology from these calcifications.

Back Pain

A number of patients on PD may develop lower back pain. Usually these individuals have alterations in body posture resulting from accentuation of lumbar lordosis due to intraperitoneal dialysate. This alters normal spinal mechanics, and leads to pain. Those factors which may contribute to adverse effects on lumbar lordosis are prior multiple abdominal surgeries, previous disc disease, spondylosis, spondylolithesis, and long-standing metabolic bone disease. Regular lower back strengthening exercises, attention to appropriate posture, the McKenzie rehabilitation program, and change to cycler therapy with the majority of treatments performed in the supine position may be effective in reducing pain.

Other Issues: Fluoride, Tendon, Oxalate

A single report has demonstrated an increase in fluoride levels in CAPD despite appreciable clearance across the peritoneum (3.1 ± 1.97 vs. 2.5 ± 1.37 μm/L). Increased serum fluoride is associated with a lower risk of osteodystrophy in ESRD.

Patients on PD can develop tendon inflammation, rupture or capsular tear. The longer a patient is on dialysis and the more severe the metabolic abnormalities, the greater the risk. These clinical events can occur independently of β2 microglobulin deposition.

Patients on PD may develop hyperoxalatemia resulting from oxalate retention. Levels of oxalate in PD patients are 3 – 5 times greater than normal. PD clears approximately 300 μM/day, approximately equal to the normally synthesized amount. Even when a steady state is achieved, serum levels are usually elevated. Usually those patients who develop hyperoxalatemia as a complication on PD are consuming excessive amounts of vitamin C; 100 mg of ascorbic acid increases oxalate by 20%. Concomitant administration of "high dose"vitamin B_6 will decrease but not normalize serum oxalate levels.

Pulmonary Complications

Patients on PD may develop a number of pulmonary complications. These include hydrothorax, pulmonary function abnormalities, pulmonary edema, bronchopulmonary infections, metastatic calcifications, and sleep dysfunction.

Hydrothorax

The prevalence of hydrothorax ranges from 1.6% [21] to 2.9% [80] to as high as 10% [98]. In many cases, patients are either placed on HD temporarily or undergo permanent transfer. Eighty-eight percent of acute hydrothorax in CAPD occurs on the right side from one day to 8 years after the initiation of PD. Seventy-four percent of patients present with dyspnea, while 26% are asymptomatic. Most patients are female, multiparous, and have been on PD for variable periods of time. Patients with polycystic kidney disease are at increased risk for hydrothorax. Peritonitis may also increase the risk, possibly related to a disruption in the continuity of the peritoneal-pleural structure. Approximately 6% of hydrothorax patients suffer peritonitis just prior to the development of hydrothorax. Several reports have indicated hydrothorax occurs after coughing. Hydrothorax can be diagnosed by the finding of a pleural effusion on chest X-ray. Further work-up consists of peritoneal-pleural scintigraphy, or contrast peritonography with non-ionic contrast (25 m/L). Thoracentesis yields fluid with a transudate protein concentration < 30 g/L, low lactate dehydrogenase (LDH), pleural glucose > plasma glucose, and the presence of both D and L lactate isomers. (Plasma normally contains only the L isomer.) Methylene blue installation, used in the past, is unreliable.

The standard approach to treatment, successful in 38% of cases, is temporary transfer to HD. Pleuradesis is required in 16%, and 46% must be permanently transferred to HD. Surgical exploration of patients with hydrothorax demonstrates localized areas of pleura separated from the diaphragm forming blebs. With the increased intra-abdominal pressure or changes in intrapleural pressure with coughing, dialysate could rupture the blebs, allowing fluid to enter the pleural cavity. Videothoracoscopy allows identification of the diaphragmatic defect. If amenable to repair, talc is placed under direct visualization, allowing even distribution over the inferior surface of the lung. Pleurodesis can also be accomplished by IP autologous blood instillation (40 mL) followed by the Fowler position for 2 days. Fibrin adhesive has also been used to repair diaphragmatic defects.

Therefore, the therapeutic options for patients suffering hydrothorax include: permanent transfer to HD; temporary transfer to HD with retrial of PD; conversion of patient to diurnal PD with an empty supine nighttime exchange; pleuradesis with talc, tetracycline, or fibrin glue; and surgical closure or repair using Teflon patches.

There has been one reported case of tension hydrothorax as a complication of continuous cycling PD. This occurred in the setting of massive hydrothorax producing hemodynamic compromise.

Respiratory Function Abnormalities

The various pulmonary function abnormalities reported in PD most likely would only affect patients with underlying parenchymal lung disease, e.g. COPD, IP pressure > 20 cm of water and a decrease in vital capacity (VC) > 25% [35]. Infusion of dialysate in PD patients without lung disease decreased expiratory reserve volume (ERV) 21% (1.00 to 0.79 L) and functional residual capacity (FRC) 12% (2.60 to 2.28 L). Inspiratory capacity (IC) increased 13% (2.08 to 2.34 L) when the abdomen was full, due to increased diaphragmatic contractility because of the elevation and lengthening of the fibers of the diaphragm [90, 91]. In another study, as PD volume increased from 0 to 3 L, FRC decreased 2.41 to 1.493 with mean total diaphragm length index increasing from 0.22 to 0.28 and diaphragm radius curvature remaining unchanged. Respiratory muscle strength increased as a function of dialysate volume, reaching its maximum after the infusion of 3 L.

CAPD patients may experience a mild but clinically insignificant decrease in carbon monoxide transfer compared to pre-dialysis or HD groups despite adequate correction of uremia and anemia. Small airway collapse with subsequent ventilation-perfusion mismatch and arterial hypoxemia may occur if the FRC decline from intra-abdominal dialysate falls below the closing volume of the lung. Two-liter dialysate volumes cause a significant reduction of alveolar partial pressure of oxygen (pAO_2) and the alveolar-arterial oxygen gradient ($A\text{-}aO_2$), but no effect on airway resistance. Subsequent diaphragmatic adaption, with a right shift in the force-length relationship, limits the “true” reduction in lung volume, pAO_2 and alterations in respiratory muscle strength during chronic dialysis.

Hospitalized infants on ventilators may be more susceptible to the pulmonary consequences of intra-abdominal fluid than adults or adolescents. Mid-dwell peak IP pressure correlates with a significant decrease in pulmonary compliance and an increase in airway resistance in infants on PD. In children on CAPD, the routine filling of the abdomen is followed by an 11% decrease in residual volume, which is not significant. Even though lung volumes are frequently reduced in CAPD, they do not change noticeably during dialysis itself. Overall reductions in inspirametric values are minor, as assessed through plethysmographic lung volumes, airway conductance and single breath carbon monoxide transfer factor.

Bronchopulmonary Infections

Patients on PD are at increased risk for bronchopulmonary infections due to depression of the humoral and cellular immune systems, reduced macrophage activity of increased interstitial lung fluid if over-hydrated, altered $A\text{-}aO_2$ gradient, and reduced ventilation in the lung base. This makes aggressive diagnosis and treatment of bacterial pulmo-

nary infections crucial to avoid significant morbidity.

Metastatic Pulmonary Calcifications

Metastatic pulmonary calcifications can occur in patients on PD. Usually these are asymptomatic and undetectable by conventional radiology methods until severe disease exists. Pulmonary calcifications occur in up to 80% of patients having undergone dialytic therapy. They may rarely evolve to pulmonary fibrosis, cor pulmonale, and severe respiratory insufficiency. Calcifications may be diastrophic, metastatic, or idiopathic associated with Ca, P, and metabolic disorders with precipitation of Ca salts within the parenchyma of the lung.

Pulmonary Edema

Pulmonary edema may occur in CAPD secondary to a number of interacting factors. The most common is prescription mismatch where the dialysis regimen does not optimally match the transport characteristics of the peritoneal membrane. Usually this occurs soon after initiation of dialysis and prior to performing the formalized PETs. Pulmonary edema occurs more frequently in the context of left ventricular failure, cardiomyopathy and acute ventricular infarction, especially if severe anemia and hypoproteinemia are present.

Sleep-related Respiratory Disorders

Sleep-related respiratory disorders in PD patients are frequent, with 73% reporting insomnia, and 52% reported unintentional napping during the day [110]. Clinically significant sleep apnea was present in 13.6% of patients. The effect of PD on sleep-related respiratory function might result from dialysate bulk load in the abdomen causing alterations in the metabolic control of respirations during sleep. In patients with typical sleep apnea, pAO_2 was significantly lower during the night for PD vs. non-PD patients. In apneic patients, higher dialysate drain volumes in the morning were correlated to lower minimum arterial oxygen saturations during the night. Individuals with documented or suspected sleep apnea should have a formal evaluation, including arterial oxygen saturation during sleep while on PD. Prospective PD candidates with a history of sleep apnea symptoms should undergo formal testing prior to starting PD.

Metabolic Complications

Acid-base Abnormalities

Approximately 50% of patients with renal failure on PD experience a number of acid-base abnormalities. Many of these are directly related to the type of dialysate used during PD. Acid-base balance (ABB) in CAPD patients can be summarized by the equation:

ABB = dialytic base gain – metabolic acid production – urinary losses – interstitial ABB.

Dialytic base gain depends on peritoneal buffer fluxes, which is the only source of buffer for CAPD patients. The net bicarbonate gain per exchange is a function of bicarbonate content in the dialysis solution, dwell time, UF rate, and arterial plasma bicarbonate [30]. While metabolic acidosis is more common in HD, PD patients may develop bicarbonate

levels < 24 mM/L (cut-off values vary 22.0 ± 4 mM/L). Metabolic acid production as a function of protein catabolic rate and dialysate base gain is the most important factor for the body's base balance. When plasma bicarbonate concentration decreases due to an increase in metabolic acid production, bicarbonate loss through standard lactate CAPD solution decreases, leading to a greater positive dialytic base gain. When an increase in daily net UF is required for clinical reasons, a decrease of dialytic base gain occurs leading to a decline in plasma bicarbonate concentration and worsening metabolic acidosis.

Chronic metabolic acidosis decreases albumin synthesis, induces negative nitrogen balance, and leads to increased protein catabolism and branch-chain amino acid metabolism. Sodium bicarbonate supplementation in PD patients increased the serum bicarbonate from 19.3 to 26.2 mM/L, thus decreasing leucine oxidation and protein turnover, and correcting acidosis [36]. PD patients using standard dialysis fluid lactate concentrations of 35 mM/L can develop mild acidosis, which activates the ATP-dependent ubiquitin proteolytic pathway. This negative buffer balance can be corrected by increasing the lactate concentration to 40 mM/L. Serum bicarbonate or total CO_2 < 19 mEq/L is deleterious to bone and muscle metabolism and is a marker of increased mortality. The frequency of metabolic acidosis is higher in patients with lower transport characteristics. Lactate gain, duration of PD, CRP and normalized protein nitrogen appearance (nPNA) were independent factors determining the arterial bicarbonate level.

Discrepancies in the reported prevalence of metabolic acidosis in PD patients is most likely due to differences in the concentrations of dialysate lactate (40, 37 or 35 mM/L) and prescribed dwell times. Dialysate/plasma (D/P) creatinine is positively correlated with gain of lactate and dialytic base, and arterial bicarbonate concentration. Since the molecular weight of lactate is 89 daltons compared to 113 daltons for creatinine, high transporters have less metabolic acidosis. The effluent bicarbonate concentration can be predicted from the patient's plasma bicarbonate concentration and the net UF rate for dwell times ≥ 4 hours or more prolonged dwell time. Bicarbonate dialysate improves acid-base homeostasis in CAPD, and future bicarbonate solutions may dramatically affect levels of protein turnover.

Peritoneal dialysis effluent pH is decreased in CAPD peritonitis even in the absence of a positive culture, provided the cell count is elevated. In gram-negative peritonitis, the peritoneal effluent is more inflamed and abnormalities persist longer resulting in a marked increase in pCO_2.

Lethal lactic acidosis from the oral hypoglycemic agent, Metformin, in a diabetic female PD patient has been reported. Moreover, D-lactate-containing dialysate may raise serum D-lactate to abnormal levels in PD. Using dianeal with a D-lactate concentration of 26 mM (range 19 – 27 mM), led to serum D-lactate levels in CAPD patients 4-fold higher than controls [4]. Usually lactate does not increase significantly unless there is severe hepatic failure leading to inadequate conversion of lactate to bicarbonate. With metabolic or respiratory alkalosis, patients on PD are unable to compensate due to the presence of lactate in the dialysate. If this occurs, patients may need HD or treatment with hydrochloride.

Electrolyte/Mineral Disorders

Metabolic alkolosis can lead to hypocalcemic tetany in PD by decreasing the amount

of Ca in the ionized form. The risk is highest in PD cases after parathyroidectomy. Pulmonary parenchymal disease, e.g. COPD, also poses a risk by predisposing CAPD patients to developing respiratory alkalosis from hypoxia with "fixed" bicarbonate levels that do not allow for an unlimited degree of hyperventilation. Treatment with O_2 or ammonia chloride may help avoid alkalemia. Lastly, low-Ca dialysate may result in alkalosis and hypomagnesemia in certain cases.

Hypokalemia

Approximately 36% of CAPD patients develop hypokalemia requiring supplemental potassium (K^+). Approximately three-quarters of the IP-administered K^+ is absorbed. Supplementation of 20 mEq/L is generally well tolerated [101]. The effect of IP K^+ concentration on serum levels depends on the D/P concentration gradient; with greater degrees of K^+ depletion, the incremental increase from IP K is smaller.

In a study of hypokalemia in CAPD patients, individuals who subsequently required K^+ supplementation had significantly lower initial serum levels (3.6 ± 0.65) vs. 4.0 ± 0.6 mEq/L), complained more of weakness, and were more likely to be African-American [55]. While different dialysis and demographic factors were analyzed, race was the most significant variable for hypokalemia warranting oral K^+ supplementation [54]. Usually oral supplementation alone is sufficient to correct the deficit. In further analyses, the presence of hypokalemia in PD could not be explained by membrane transport differences, protein intake, concomitant medication or small molecule clearance.

Hyponatremia

Recurrent hyponatremia in anuric infants undergoing PD has been reported. Hyponatremia has been observed especially in infants and young children due to low sodium (Na^+) intake (such as infant formula), renal Na^+ losses, inadequate UF, or obligate Na^+ losses that occur at UF rates necessary to maintain fluid balance in combination with a low-sodium diet. The ratio of Na^+ in the ultrafiltrate to the serum (sieving coefficient) is usually < 1. The initial decrease in dialysate Na^+ during UF indicates Na^+ sieving across the peritoneal barrier. Dialysate Na^+ decreases with 4.25% glucose dialysate, while plasma sodium increases slightly. With very short dwell times utilizing hypertonic glucose, Na^+ removal is lower relative to fluid removal, potentially resulting in hypernatremia. Dialysate sodium may actually decrease during longer dwell periods, suggesting that sodium crosses the peritoneal membrane to a lesser degree than water and more water than sodium is removed in over-hydrated patients.

Adult patients with labile blood glucose, and those on tricyclic antidepressants or clonidine may experience stimulated thirst and increased water intake leading to hyponatremia. Thirst from stimulation of the renin-angiotensin system can also lead to hyponatremia. Notably, the renin-angiotensin system is functioning at a higher level in PD patients than HD patients. Overly rapid correction of acute hyponatremia should be avoided, as it can lead to central pontine myelinosis.

Hypermagnesemia

Hypermagnesemia (1.04 – 1.29 mEq/L) is frequently observed in CAPD patients, and a highly significant inverse relationship exists between immunoreactive PTH and magne-

sium concentrations. The reduction or removal of magnesium from dialysate solution results in normalization of elevated serum magnesium concentration. Decreasing PD solution magnesium concentration from 1 – 1.2 mEq/L to 0.5 mEq/L resulted in clinical hypomagnesemia in 64% of patients, warranting magnesium supplementation. Therefore the concentration of magnesium in the dialysate may be an important determinant for the risk of hypomagnesemia on PD.

Sulfate Clearance

Inorganic sulfate clearance is similar to the clearance of creatinine and phosphate, but significantly less than urea. Sulfate deficits in PD have been reported due to losses in stool, and losses of sulfate in other forms (e.g. taurine, phenol, and sulfate).

Malnutrition

A number of factors are be involved in the development of malnutrition in patients on PD. Anorexia may result from several different factors, including GI tract dysfunction (secondary to DM or medications), and abnormalities in basic metabolic pathways/brain metabolism, either directly or indirectly related to dialysis procedures [48]. However, calories derived from the glucose dialysate load in PD do not suppress appetite as previously believed. Anthropometric and biochemical evidence of protein malnutrition have been observed in 18 (51%) of CAPD patients. Fifty-five percent of PD patients in the CANUSA study were malnourished [69].

Plasma amino acid levels are lower in PD vs. HD patients, although the intracellular amino acid pattern is less abnormal. It is unclear what effect dialysis dose has on amino acid abnormalities. Protein loss in PD is a contributing factor to lower plasma amino acid concentrations. Total amino acid losses over a one-week period average 61.8 ± 14 mM for HD and 38 ± 13 mM for CAPD. Levels of total amino acids, essential amino acids, non-essential amino acids, and branched-chain amino acids were lower in PD than HD.

Because protein-calorie malnutrition is a strong predictor of morbidity and mortality, early intervention utilizing protein supplements or enteral feeding should be undertaken. Amino acid solutions and recombinant human growth hormone (rhGH) have the potential to improve nutritional status of CAPD patients. Insulin may be required to treat hyperglycemia in patients receiving increased glucose loads from a combination of PD and TPN. Malnourished patients on PD receiving parenteral nutrition are at increased risk to develop hypophosphatemia. Phosphate replacement should be supplied cautiously in patients with hypomagnesemia and hypocalcemia due to the risk of bilateral vocal cord paralysis. Severely malnourished patients on CAPD undergoing tube feedings may develop "re-feeding syndrome". This syndrome is associated with clinically significant shifts in P, magnesium, and K^+ from extracellular to intracellular spaces.

Chronically malnourished patients whose cardiac muscle is nutritionally depleted cannot deal with the increase in circulatory demands caused by the initiation of aggressive nutritional support. These individuals may develop acute respiratory distress unless volume is closely controlled. In an earlier report, low-dose intramuscular (IM) nandroline decanoate for ≥ 3 months (100 to 200 mg IM/month) exerted a definite anabolic effect in 9 malnourished PD patients. Megestrol acetate has also been used in PD, both in low- and high-dosages (40 – 800 mg). Its major com-

plications occur with increasing doses: adrenal insufficiency, glucocorticoid deficiency, and thrombosis.

Growth Abnormalities

While children on long-term dialysis experience growth abnormalities, these may occur less frequently on PD than HD, whether or not rhGH is given. Proposed reasons are improved urea control, less acidosis, and caloric support from dialysate glucose. However, protein losses from PD may impair normal growth, especially in infants, and may contribute to permanent loss of growth potential. Recombinant human growth factor-1 (rHuGF-1) and rhGH both have demonstrated beneficial effects on nutritional status in short-term studies. These may be of use in children who demonstrate a decreased ability to grow on PD.

Uncontrolled Diabetes/AGE

Local generation of AGE occurs in the peritoneal membrane. A "washing out" of AGE from the peritoneal membrane takes place after a 12-hour dwell period, when the dialysate concentration of AGE is greater than the plasma concentration. Positive staining for AGE has been documented in the interstitium of the mesothelial layer in the peritoneal membrane. In other studies, there was an observed 200% increase within a 4-hour dwell cycle due to in situ glycation. Peritoneal protein contained a 2 – 4 times greater concentration of AGE pentosidine at all equilibration time points. Dialysis glycolated albumin is linearly related to the glucose concentration of both dialysate and in vitro phosphate-buffered saline. AGE formation, but not glycation, decreased as a function of dwell time, possibly attributable to peritoneal membrane clearance. Transplantation is the best therapeutic modality to normalize both pentosidine albumin linked or pentosamine-free membrane changes.

Worsening blood glucose control can result from the glucose load on PD. Tolbutamide, glipizide, glyburide, and rezulin are oral agents used in controlling hyperglycemia in PD. Further control can be accomplished by the use of IP or subcutaneous (SC) insulin (NPH, regular, 70/30, or 50/50). The mechanism for insulin dosing is different in automated PD than CAPD. Several different techniques for insulin dosing have been proposed. For patients with a life expectancy > 3 years, the target control goals are blood glucose 110 – 160 mg/dL, HbA_1C 7 – 8.5%, and up to 1 – 3 episodes of mild hypoglycemia/week. Magrey et al. [66] reported the correlation of HbA_1C and fasting blood glucose in PD was 2.884 ($p < 0.0001$). Most patients require a sliding scale for optimal control. Blood glucose > 500 mg/dL requires multiple SC doses or IV insulin treatment. A significant percentage of patients on automated PD require SC insulin in addition to IP insulin, whereas those on CAPD can usually be controlled with IP insulin.

Hormonal Abnormalities

Multiple hormonal abnormalities occur in patients on PD [62]. Sexual dysfunction is common in patients on PD, especially in males, and may be related to medications, local disease processes, or systemic disease processes (e.g. DM, vascular or neurologic disease). Patients have decreased testosterone levels and spermatogenesis. An increased fre-

quency of anovulation and low fertility rate in females is related to hormonal imbalances, such as derangements in the positive feedback between estrogen and the hypothalamic gonadotropin secretion. Children may have delays in puberty or central precocious puberty on maintenance PD, the latter being reversible with transplantation. While EPO treatment may improve sexual function, hormonal abnormalities still persist in most patients. Abnormal thyroid function persists on PD with decreased serum triiodothyronine (T3) and total thyroxine (T4), although thyroid-stimulating hormone (TSH) is not elevated. Thyroid-binding globulin, T4, and T3 are lost in the dialysate. Plasma renin and aldosterone are normal or mildly increased in PD. Plasma-18 hydroxycorticosterone is higher and may explain a decreased incidence of hyperkalemia with more incidences of hypokalemia in PD.

Obesity

Weight gain can be a complicating problem on PD. The kilocalorie load from PD is approximately 8 kcal/kg/day, yielding a total daily gain of 35 – 42 kcal/kg/day. This results in a significant weight gain in certain obesity-prone patients. The approach to obesity in PD is problematic. While newer medications have been attempted, their safety and efficacy in renal failure is unproven. Attempts at lowering percent glucose delivered are difficult since energy consumption may be low with inactive individuals.

Neurologic Complications / Psychological Complications

Traditionally a number of neurologic complications can occur in uremic patients on dialysis. Both HD and PD are associated with at least 3 distinct disorders of the central nervous system (CNS): dialysis disequilibrium syndrome, dialysis dementia, and progressive intellectual dysfunction. Specific abnormalities in cerebral metabolism, cognitive changes, psychological abnormalities, neuropathy and autonomic dysfunction can also occur on PD.

Cerebral Metabolism

Cerebral metabolite abnormalities have been identified in patients on dialysis [71]. CAPD patients demonstrate increased choline and myo-inositol levels compared to HD patients. Studies using localized short echo-timed proton magnetic resonance spectroscopy to measure cerebral water and metabolites in humans demonstrated abnormalities consistent with osmotic dysregulation in PD. Abnormal choline/creatinine ratio and N-acetyl aspartate concentration also occur in PD.

While these disorders exist with renal failure, they appear uncorrected by dialysis. Furthermore, the abnormalities affecting the cerebral metabolism are not explained by the effects of specific types of dialysis. More clinically apparent abnormalities, like dialysis encephalopathy in PD, are most likely attributable to impaired response of cerebral osmolites. CAPD may be more effective than HD in reversing uremic encephalopathy by mechanisms unrelated to serum creatinine and urea levels.

Psychological Abnormalities

Both cognitive and psychological abnormalities occur in children and adults on PD. Intriguingly, CAPD patients had consistently better cognitive function than the chronic HD subject group in several studies. A number of tests [50], including the Patient-Related Anxiety Scale (PRAS), Beck's Depression Inventory (BDI), Kupfer-Detre System II Somatic Symptoms Scale (KDS/II) have supported the relationship between abnormalities in psychological status and outcome. Significantly higher complication rates for CAPD patients are correlated with higher scores. Those with the highest scores have more symptoms of depression, anxiety, somatic symptoms and overall poorer quality of life. Fukunishi noted that 65.4% of children demonstrate a separation anxiety disorder or deterioration of psychological adjustment when on home PD [32]. The global intelligence quotient measure by the Wechsler and Bender tests demonstrates that the majority of children have average intelligence (77%), and high verbal IQ, and yet the performance IQ is significantly lower. Less anemia on PD than HD may contribute to PD patients' higher test scores, since anemia adversely affects cognitive performance.

Noncompliance may be observed in a significant percentage of PD patients. The term "noncompliance" represents a complex set of behaviors and interpersonal relationships with family, physician, nurse, and others which has important cultural and ethical considerations. The spectrum of noncompliance can include refusal to accept specific therapeutic recommendations to the most drastic form, which is withdrawal from therapy.

A specific number of psychological factors has been shown to have an impact on compliance in PD patients. These include patients' beliefs about their health behavior, locus of control and self-efficacy, family problems, and social support. However, there is a relationship between compliance and perceived health outcomes in dialysis overall and particularly in PD patients because of their direct involvement in their overall well-being and adequacy of care.

Indices of hyperparathyroidism were significantly associated with headache, joint pain, dyspnea, and nausea. The severity of these somatic complaints seen in patients on PD are connected to the indices of disease-effective disorders and perceived quality of life.

Multiple Neuropathies

A number of different types of neuropathies develop in PD patients, the most dramatic of which is rapidly-evolving inflammatory demyelinating polyneuropathy, also referred to as "pseudo-Guillain-Barré syndrome". The onset of this disorder is from 4 – 10 weeks after beginning PD. This acute or subacute syndrome is characterized by generalized limb weakness developing over days or weeks associated with severe imbalance, diminished reflexes, and numbness. The natural history is significantly different than diabetic or uremic neuropathy. Another form is a more chronic or indolent process, termed chronic inflammatory demyelinating polyneuropathy. Both of these types of polyneuropathy can occur in PD. The mechanism is unclear. Demyelination may result from T cell-mediated destruction of myelin sheaths mediated by tumor necrosis factor (TNF) α, increased immune stimulation and a loss of a myelin-stabilizing factor. The progression of neuropathy may be halted in some cases by significantly increasing the level of middle molecule clearance, although higher doses of dialysis usually do not lead to improvement in symptoms. A reversal of symptoms, or a cessation in symp-

tom progression may occur with transplantation. The above polyneuropathies are characterizes by axonal degeneration with secondary segmental demyelination. Several subclinical disorders of auditory (eighth) nerve function are part of the axonal uremic neuropathy that may occur in patients on PD. This may explain the susceptibility to neurotoxic drugs, including antibiotics.

Peripheral neuropathy can occur in a large number of diabetic patients who have been on PD for > 5 years. Most likely there is some relationship between the adequacy of dialysis and the risk for developing progressive diabetic nephropathy. In diabetes and uremia, the neuropathy tends to be distal, symmetric, sensory more than motor, and involving the lower extremities more than the upper. The development of uremic motor neuropathy is a medical emergency warranting early attention to the dialysis prescription and consideration for combination therapy with either HD or hemodiafiltration (HDF) and PD, to achieve total creatinine clearances per week of > 130 – 150L/wk and/or transplantation prioritization.

A specific type of familial, amyloid polyneuropathy can occur and is characterized by peripheral nerve amyloidosis and sexual dysfunction. Both patients on HD and PD may develop this abnormality.

Autonomic Dysfunction

Autonomic function is significantly reduced in CAPD patients compared to controls [47]. A reduction of sympathetic activity in the limbs and cardiovascular autonomic impairment are seen. Defective regulation of heart rate, due mostly to afferent limb abnormalities, is more common than damage of reflex blood pressure control. There was no difference in the electrophysiological parameters in patients with HD or PD. However, autonomic dysfunction may occur to a greater degree in HD than PD. Impairment of autonomic function in the heart and peripheral circulation may have consequences to overall cardiovascular status, and cardiac dysautonomia may be associated with high incidence of sudden death in both diabetic and uremic patients.

Gastrointestinal Complications

Pancreatitis

The risk for pancreatitis is increased in patients on PD compared to HD, and is a significant cause of increased morbidity in CAPD [15]. Abdominal pain, nausea and vomiting with negative peritoneal cultures or without clinical evidence for peritonitis should suggest the diagnosis of pancreatitis. Contributing factors for pancreatitis include hypertonic dialysate [> 50% of exchanges using 4.25% (3.86%) glucose dialysate], hypercalcemia, malnutrition, gall bladder disease, and time on dialysis > 23 months. An edematous and/or calcified pancreas (Figure 16) on CT is more reliable than pancreatic enzyme elevations. A serum amylase > 3 times the upper limit of normal, or lipase > 4 times the upper limit of normal have a strong correlation with true pancreatitis. The enzyme elevations in HD are higher in the setting of pancreatitis than those that occur on PD. Dialysate amylase is increased to the high normal or above normal range. A dialysate amylase > 100 units/L is suggestive of intra-abdominal pathology, i.e pancreatitis, rather than peritonitis. Serum concentrations of pancreas-specific P3 isoen-

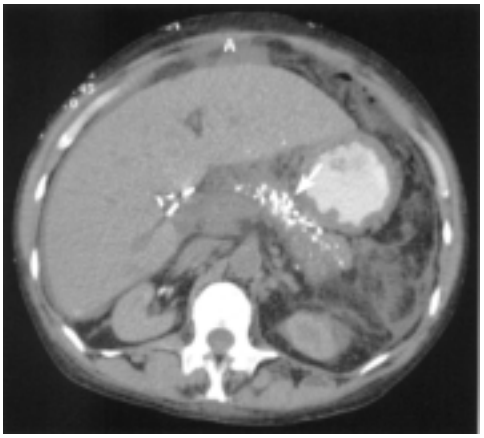


Figure 16. This CT scan demonstrates an edematous calcified pancreas in a CAPD patient presenting with acute pancreatitis.

zyme are increased in approximately 30% of asymptomatic ESRD patients. The treatment of pancreatitis should entail symptomatic care, nasogastric suction, and possible temporary discontinuation of PD.

Motility Abnormalities on PD

Unrecognized gastroparesis may have a critical impact on the morbidity of PD patients. Both diabetic and nondiabetic patients may present with dysmotility and/or delayed emptying while on CAPD. Type 1 diabetics exhibit diabetic gastroparesis more than Type II diabetics (70% vs. 37%) [27]. Patients with longer durations of DM, higher frequency of orthostatic hypertension, history of enteropathy, vascular complications (acute MI, blindness, amputation), malnutrition with DM, poor glycemic control, and a history of increased hospital days with Type 1 diabetes are more likely to have gastroparesis [9]. Eighty-eight percent of patients on PD with gastroenteropathy demonstrate abnormal gastric emptying times. Solid phase label with technetium^{99m} and liquid phase labeled with ^{111}indium are used to diagnose motility abnormalities. Despite abnormal solid emptying, many patients do not suffer symptoms.

Fifty-five percent of PD patients had abnormal carbon^{14} urea breath tests indicative of delayed gastric emptying [63]. Foregut motor dysfunction, and abnormal gastric antral electrical control with gastric dysrhymthia can occur. All CRF patients with anorexoria and vomiting in one study had ≥ 1 disorders of foregut motility. Fasting serum gastrin levels, gastric myoelectrical activity, and bioelectrogastrogram results demonstrated abnormalities, which were not always corrected by dialysis. Clinically, if a CAPD patient has lower esophageal sphincter pressure abnormalities with 2-L dialysis volumes, there is a greater risk for dysmotility symptoms. Thus, the demonstration of an incompetent lower esophageal sphincter pressure may bode poorly for patients wanting to use PD.

Gastric emptying abnormalities in PD are improved with erythromycin elixir or metoclopramide. In one report, gastric emptying time improved from 122 minutes to 12 minutes [24]. Erythromycin inhibits the binding of the GI peptide motilin to its smooth muscle receptor, thus improving symptomotology. Erythromycin doses of 100 mg/2 L administered IP can be given for long-term treatment without apparent side effects. Some reports of tolerance to erythromycin suggest alternating erythromycin (3 weeks) with metoclopramide (1 week).

Malnutrition due to gastroparesis can also occur in nondiabetic patients on PD. Therefore, even nondiabetic patients with persistent decreases in appetite or malnutrition should have radionucleotide gastric emptying scans, both to diagnose gastric abnormalities and to monitor treatment success with promotility drugs. Early satiety or poor appetite in the

absence of nausea and vomiting could also be caused by gastroparesis. Cisapride, while helpful in nonuremic patients with gastroparesis, may contribute to the development of arrhythmias in patients on dialysis and should be avoided.

Gastric Reflux/Bloating

Patients on PD may develop gastroesphageal reflux. Supine lower esophageal sphincter pressure can be checked by esophageal monometry or pH monitoring after instilling 2 L of dialysate. There appears to be no difference in supine vs. sitting positions with respect to lower esophageal sphincter pressure. However, there is an increase in total reflux score (symptomatic reflux, nausea, vomiting, epigastric discomfort) in symptomatic PD patients. Furthermore, the total treatment time wherein the pH was < 4 was significantly greater than anticipated when 24-hour esophageal pH monitoring was utilized.

Non-obstructive Mesenteric Ischemia

Non-obstructive mesenteric ischemia (NOMI) occurs in approximately 30 – 40% of nondialysis patients with mesenteric ischemia or infarction wherein no gross arterial or venous obstruction can be found. NOMI occurs in patients with low cardiac output states from circulatory collapse associated with hypovolemia, cardiac dysfunction, arrhythmias, hypoxia or hemoconcentration (HCT > 41.5). Previous reports have shown that digitalis administration has resulted in preferential mesenteric vasoconstriction in high-risk patients. There have been several reports of NOMI occurring in patients undergoing PD, however the role played by intra-abdominal shunting of blood is unclear.

Ascites

Chylous ascites may complicate PD either soon after starting treatment or in conjunction with an additional surgical procedure. This rare clinical entity is usually secondary to disruption of a lymph channel or lymphoma. The ascites is significantly cloudy or milky, with characteristic laboratory findings of: chylomicrons on lipoprotein electrophoresis, triglyceride levels of dialysate > plasma, and positive Sudan black staining of dialysate supernatant. In 230 cases of chylous ascites in PD patients, malignancy was encountered in only 2 cases. A precise diagnosis was difficult to establish in the remainder. The chylous effusion in 7 cases appeared secondary to sclerosis, chronic pancreatitis, systemic amyloid or cardiac failure; 3 cases were likely due to microtrauma from a Tenckoff catheter. Ascites lasted for > 2 years in 4 cases and required long-term nutritional support. Patients may be able to continue on PD if they are able to maintain a stable nutritional status.

Gastrointestinal Bleeding

GI bleeding is more common in HD than PD patients. Bleeding may result from uremia, iatrogenic causes, underlying systemic disorders, or an unrelated GI disease. Gastritis, duodenitis, amyloidosis, warfarin, increased heparinization, coexistent GI disease, and angiodysplasia are the most common causes for GI bleeding. Angiodysplasia is more common in HD, and is associated with vascular calcifications, constipation and possible chronic venous hypertension. Angiodysplasia should be suspected in patients with

HIV, Karposi's sarcoma, CMV colitis or non-Hodgkins lymphoma. Endoscopy is helpful both in diagnosis and treatment. Erosive gastritis occurs in approximately 30% of dialysis patients with GI bleeding. The remaining cases are due to colonic polyps, esophagitis, melanosis, diverticuli, erosive duodenitis, or gastric ulcer. Patients on PD with intractable vomiting and abdominal pain can present with a gastric ulcer due to *Helicobacter pylori* infection. These patients should be treated with metronidazole, imiprazole, and clarithromycin.

Hepatic Complications

A number of different liver parenchymal diseases may present in dialysis patients including hepatitis C, hepatitis G, and hepatitis B. Both hepatitis B and C are more commonly transmitted through HD than PD, with a risk hazard ratio of 5.7. Biochemical tests are poor indicators of liver disease progression; liver biopsy is indicated as the definitive means of evaluating PD patients with positive hepatitis C viral (HCV) antibodies, as approximately 20 – 25% of HCV RNA carriers in the US develop cirrhosis. The prevalence of anti-HCV among CAPD patients ranges from 1.8 – 15.4%, with 16.4 – 46.7% positivity in HD. Enzyme-linked immunosorbent assay (ELISA) II testing is more sensitive than Recombinant Immunoblot Assay II (RIBA II): positive results in 52% of HD and 14% of PD, vs. 38% HD and 11% of PD patients, respectively [16]. Reports from Singapore demonstrated HCV positivity by polymerase chain reaction (PCR) in 41.5% of HD and 12% of PD patients.

Strict compliance with universal infectious disease precautions from the Center for Disease Control is mandatory for both HD and PD patients. While the duration of PD did not affect risk, transfusion requirements may be a risk factor. HCV infection was observed to be significantly more common in female PD patients; and correlated to events occurring before the start of PD therapy. Therefore, PD should be considered as low risk for HCV infections compared to HD. Increased HCV seropositivity in Ashkenazi Jews points to ethnic factors predisposing to HCV transmission, again with a higher prevalence in patients on HD vs. PD.

The frequency of HCV antibody was significantly higher in hepatitis B-positive patients. Hepatitis B virus (HBV) may not cause significant serum amino transferase elevations in all patients. HBV can be transmitted in the dialysis setting through blood transfusions and environmental surfaces. However, dialysis ultrafiltrate or PD dialysate seems to be an improbable source of HCV dissemination in the dialysis setting. A significant association exists between HBV and the presence of anti-HCV antibodies. Common epidemiologic routes for HCV infection may exist in Hong Kong, China and East Asia. Hepatitis G is a novel RNA virus of the Flavividae family occurring in both HD and PD. The prevalence of HGV infection is similar in HD and PD.

Esophagitis

Esophageal infections can occur especially in diabetic and immunocompromised patients on PD. Diabetic patients, especially those with persistent hyperglycemia, have an increased risk for *Candida*-induced esophagitis, as do alcoholics and elderly patients. Esophageal infections could be due to *Candida*, herpes simplex virus, cytomegalovirus (CMV), and *Mycobacterium tuberculosis*. Dysphagia (difficulty swallowing) and odynophagia (pain on swallowing) may occur, but the lack

of these symptoms should not be used as evidence against esophageal infection. Nausea and vomiting occur in 42% of CMV esophageal infections, whereas weight loss is more common in CMV, tuberculosis (TB), and HIV. Oral lesions are present in 27 – 37% of patients with infectious esophagitis.

The treatment is dictated by the cause and severity of the infection. Nonabsorbable metizole may be helpful. Clotrimazole (nonabsorbable imidazole) 10 mg five times/day, or oral nystatin (nonabsorbable polyene) to disrupt the fungal membrane may also be effective.

Dermatitis Complications

Pruritus

Uremic pruritis affects 50 – 90% of PD and HD patients. Robertson et al. reported the percentage might be somewhat higher in PD vs. HD (61.9% vs. 53.9%) [93]. Pruritis usually starts approximately 6 months after initiation of dialysis therapy. Uremic pruritis may present in either of two distinct patterns: episodic, mild, and localized to the back, dialysis catheter site, face or legs; or generalized and intractable. The actual mechanism for pruritis is unclear. Histologically, there is atrophy both in the sebaceous glands and in the secretory and ductal portions of the eccrine sweat glands. Reduced stratum cornium hydration levels correlate with the degree of pruritis in PD. Usually pruritis occurs in the setting of secondary hyperparathyroidism where divalent ion abnormalities are higher coinciding with iron deficiency and, in some cases, hypervitaminosis A. Specific proteases, leukotrienes, prostaglandin E, and histamine H_2 receptor abnormalities play a role. Theoretically, the higher degree of middle molecule clearance in PD should provide for less pruritis than HD, assuming specific middle molecules play an etiological role in initiating pruritis. While Morton et al. found 27% of HD patients and 54% of PD patients complained of pruritis, other studies have noted no difference in the incidence of pruritis by dialysis modality [74]. Regular emollient use produces a marked reduction in severity of pruritis. Ultraviolet phototherapy may also provide clinical improvement in some patients resistant to standard approaches. Ondansetron (4 mg twice daily PO) may be an effective safe treatment for uremic pruritis in PD.

Calciphylaxis

Calciphylaxis is a disorder characterized by vascular calcification and tissue necrosis. These extremely painful, violacious, and necrotic ulcerative lesions are associated with mottling and gangrene of the extremities (Figure 17). These ulcerative changes can occur over arteries or on the extremities in association with increased PTH, deep Ca skin deposits, and severe hyperparathyroidism especially in DM. Histologic findings may be segmental requiring deep elliptical biopsies to identify Ca deposits. Soft tissue calcifications characterized by tenderness with extensive nonulcerative, large, hard, subcutaneous plaques in the calves and soft tissues may also occur. Bone scanning is positive for Ca deposits, and 75% of the patients have a high Ca-P product.

Other Dermatidites

Recently several patients on PD have developed a hypersensitivity reaction to the glucose polymer, icodextran, characterized by a

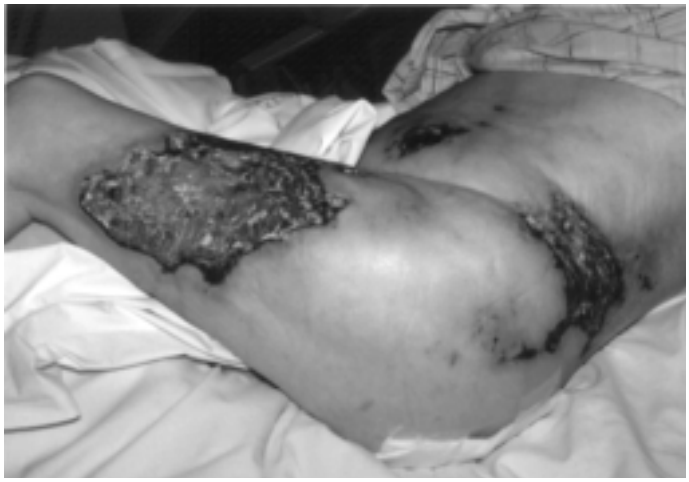


Figure 17. These ulcerative, painful, necrotic lesions in the upper thigh characterized the development of calciphylaxis in this CAPD patient.

pruritic sometimes scaly, exfoliative rash. A case report describing phenytoin toxicity causing secondary porphyria cutanea tarda in PD has been reported.

Hematology/Oncology

Anemia/Red Blood Cell Metabolism

Anemia and complications from its treatment with recombinant human erythropoeitin (rHU-EPO and iron), may occur in patients on PD. While there is an increase in endogenous EPO production in patients on PD compared to HD, the vast majority still require rHU-EPO therapy for anemia. Fifty-five percent of patients on EPO required initiation or an increase in antihypertensive therapy, compared to 19.6% of patients on placebo. Navarro et al. demonstrated in a small group of patients on PD that rHu-EPO requirements necessary to maintain a stable hemoglobin concentration were higher for patients on angiotensin converting enzyme (ACE) inhibitors [76]. The effect of rHu-EPO on peritoneal transport characteristics is unclear. A significant reduction in the levels of protein S and protein C may result from rHu-EPO and could potentially increase thrombotic events.

Dialysate may adversely affect RBC metabolism in PD. Standard dialysate may interfere with the Emden-Meyerhof pathway, the main glucose-utilizing route in the RBC. A damaging action by lactate dialysate on bicarbonate buffering necessary for normal RBC metabolism may occur. High lactate concentrations acutely inhibited the key enzymatic steps of glycolysis, leading to a significant decrease in glucose consumption and adenosine triphosphate (ATP) production. Decreased pH levels observed in lactate-incubated RBC were shown to inhibit observed G-6-PD activity.

Uremia may modulate RBC membrane cation transport, although neither PD nor HD improves this defect. The abnormalities in transport include K^+/chloride co-transport activity, amiloride/Na^+ efflux, and decrease in Na^+-K^+ pump activity.

Peritonitis may inhibit in vitro erythroid colony formation contributing to a worsening in anemia or resistance to rHu-EPO. Seemingly, endogenous pyrogens, such as interleukin-1 (IL-1) and tumor necrosis factor (TNF) also inhibit erythyropoiesis. Additionally, a circulating soluable factor inhibiting erythyropoiesis may contribute to the decreased EPO response observed during peritonitis. Iron saturation may be a good indicator of rHu-EPO requirements and responsiveness in PD patients with anemia [49]. Achieving higher iron saturation levels than the currently accepted 20% may further decrease rHu-EPO requirements in PD patients. IV infusion of total dose iron is superior to oral iron in the treatment of anemia in PD, achieving higher HCT (36.0 ± 1.0 vs. 34.4 ± 1.1). Patients on PD who have low iron saturation may develop worsening anemia despite rHu-EPO.

Platelet Abnormalities and Bleeding Diatheses

Patients on PD exhibit a marked increase in the levels of reticulated platelets compared to normal patients. The presence of increased reticulated platelets may indicate platelet hyperreactivity and accelerated platelet turnover; increased platelet turnover is usually associated with uremia [41]. The percent of reticulated platelets in PD vs. normal was 6.96 ± 0.68% vs. 2.77 ± 0.17%; the mean platelet count, however, was normal. The mean percent of reticulated platelets was greatest in HD (8.2 ± 0.36%). There does not appear to be a difference in percent of reticulated platelets between diabetic and nondiabetic patients on PD. The increased turnover rate may contribute to the acquired platelet defect and risk for uremic bleeding. Hypoalbuminemia in CAPD may also play a role although the actual mechanism is unclear.

Abnormalities of platelet surface glycoproteins GPIb and GPIIb/IIIAa (receptors for von Willebrand factor and for fibrinogen) may be involved in uremic bleeding (defect in primary homeostasis) in PD. These values are normalized in PD suggesting better homeostasis and less bleeding if patients are properly dialyzed.

Coagulation Abnormalities

The dialysis procedure can potentially affect both coagulation homeostasis and normal fibrinolysis. Procoagulant markers and fibrinolytic parameters are higher in PD than HD. However, HD increases procoagulant markers significantly over baseline [2]. CAPD patients demonstrate significantly higher levels of factors VII, IX, and X; antithrombin III; protein C; and protein S compared to HD. Furthermore, CAPD patients may have shorter prothrombin times. Enhanced fibrinolysis may be a natural protective mechanism against thrombosis. It is intriguing that a positive correlation exists between abnormalities in hypercoagulability parameters, secondary fibrinolysis, and serum lipids. Patients who demonstrate higher fibrinogen, or higher levels of specific factors in conjunction with abnormalities in lipid metabolism, may have a greater risk for underlying atherosclerosis. This increased risk may contribute to limb ischemia and cardiovascular ischemia.

Mesothelial cells play an important role in determining the fibrinolytic activity of the peritoneum in vivo and may prevent fibrous exudates and fibrin deposition in the peritoneal wall. This function may also decrease adhesion formation. Mesothelial cells express

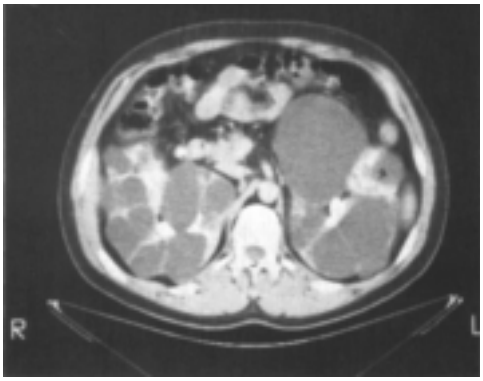


Figure 18. This CT scan demonstrates a renal cell cancer arising from the superior aspect of the left kidney in a patient with polycystic kidney disease on CAPD for five years.

plasminogen activators and inhibitors. Platelets with high PAI levels usually have positive D-dimers. Thus, low D-dimers in the peritoneal dialysate indicate a block in fibrinolysis, and heparin therapy is highly recommended. D-dimer levels may also be able to identify patients who benefit from heparin therapy during peritonitis or increased imbalance between activators and inhibitors in the peritoneal space.

Neoplasia

Speculation has existed for a number of years that uremic patients have an increased risk for malignancies. There are several factors which may increase the risk of cancer in patients on PD, or dialysis in general, including impaired function of the immune system, impaired antioxidant defense mechanisms, accumulation of carcinogenic compounds partly due to impaired renal elimination, and the risk for chronic infection and inflammation. Reports delineating the cancer risk in HD patients are more common, most likely because of the increased numbers of patients on HD worldwide compared to PD. HD patients have a risk of developing malignant tumors that is several times that of the general population. Because both sets of patients are uremic, and uremia itself may have a risk potential for cancer development, PD patients may have a higher risk as well. From 1982 through 1990, 21 urologic cancers were discovered in uremic patients from a single center [60]. Nine of 21 patients were on HD and 1/22 on PD. The standardized incidence ratio of kidney cancer in chronic HD was 24.1 ($p < 0.01$) and that of bladder cancer was 16.4 ($p < 0.01$). Hematuria was the most common presenting feature despite the fact that most patients were anuric. A further study examining the incidence of cancer in a regional dialysis and transplant registry reported a total of 479 cases of cancer, including primary cancers of the liver, kidney, and thyroid; lymphoma; and multiple myeloma [12]. There does appear to be an excess of renal cell and liver carcinomas or lymphomas in patients receiving renal replacement therapy. Acquired renal cystic disease in patients with PKD may progress to renal cell cancer (Figure 18). However, because the numbers still are small, routine cancer screening in ESRD is presently a relatively inefficient allocation of resources. The findings overall highlight the importance of considering a patient's competing risks to survival in designing screening strategies and other interventions targeted to ESRD patients. With reference to PD, specific tumors may, in fact, metastasize to the peritoneum. These include adenocarcinoma of the ovaries, stomach, colon, breast, pancreas, and lung, along with lymphoma and sarcomas. Metastatic cancer is by far the most common peritoneal tumor detected in PD patients.

Transplantation Complications and Immune Defects in PD

Graft Rejection

A number of reports in the literature have examined the difference in graft and patient survival in individuals treated with either HD or PD. Patients on CAPD may in fact have a more normal immune response than HD patients, and this may make them more immunocompetent. To test this theory, several studies have examined graft survival in PD patients who have subsequently undergone renal transplantation. Overall the rate of graft and patient survival appears to be similar between HD and CAPD [23]. The rate of graft loss due to infection may be higher for recipients who were under dialyzed pretransplant irrespective of dialysis modality. Since a significant percentage of PD patients may not achieve target clearances due to loss in residual renal function and inadequate prescription adaption, the potential risk of infection could be increased compared to HD patients. Perez Fontan reported the incidence of acute rejection was similar in both HD and PD, and that PD patients demonstrated lower rates of delayed graft function after renal transplant than a matched control group of patients on HD [84].

Post-transplantation Infection

In pancreas-kidney transplant patients, the incidence of peripancreatic abscess formation was higher in those dialysed pre-transplant with PD than HD (40 vs. 14%), with *S. epidermidis* being the most common pathogen. Douzdjian and Abecassis reported 5% peritonitis and 2.5% CESI rates in PD patients post-transplant [26]. There does not appear to be any difference in nonperitonitis-related infections between HD and PD patients in the postoperative period. Nutritional status, adequacy of dialysis, and time since prior bouts of peritonitis and CESI all have a direct impact.

The risk of developing post-transplant infections linked to the presence of the PD catheter continues to generate concern. In most studies, the persistence of the PD catheter after kidney transplantation has produced no infection or other complications. Catheters can even be safely used during acute rejection or primary graft nonfunction for dialysis. Potentially PD catheters represent an additional source of infection following transplantation if left in place for extended periods of time. Therefore, the catheter may be left in place for the first few weeks following transplantation, however, it should be removed by 3 months after transplantation because of the increased risk of catheter-related infections. Some clinicians suggest removing the catheter at the time of hospital discharge to decrease infection risk.

Renal Allograft Thrombosis

Several studies reported an increased incidence of renal graft thrombosis in CAPD compared to HD patients (7.3 vs. 3.6%) [28, 108]. A more recent study in 827 cadaveric recipients documented vascular thromboses in 4.7% of PD and 6.1% of HD patients, with no difference in the incidence of arterial and venous thrombosis by modality. Graft recipients may require detailed coagulation studies preoperatively to design effective coagulation prophylaxis, especially in cases where allograft harvest will be performed laparoscopically. There appears to be little difference in transplant characteristics, hematologic parameters, immunosuppressive therapy, graft-

ing anatomy, or preservation techniques in those patients who develop renal graft thrombosis. However, several reports associated graft thrombosis with advanced age of donor, use of the right kidney, protracted cold ischemia, delayed graft function, and previous thromboembolic events in the recipient. The presence of anticardiolipin antibodies and certain diseases such as systemic lupus erythematosus (SLE) may be associated with an increased risk of thrombosis.

Post-transplant Ascites

Symptomatic ascites can occur following the discontinuation of PD after transplantation. If the serum to ascites albumin concentration gradient or albumin gradient is > 11 gm/L, some degree of portal hypertension is likely. If the serum albumin gradient is < 11 g/L, then peritonitis, an inflammatory process, or malignancy should be considered. The causes of ascites after transplantation in PD patients include increased net UF pressure in the peritoneal capillaries, increased permeability of the peritoneal membrane to macromolecules, and decreased lymphatic absorption. These are contrasted to the causes of ascites in nonrenal patients, which include fluid overload, functional or structural changes in the peritoneal membrane and lymphatic drainage, heart failure, hypoalbuminemia, pancreatic insufficiency, and hyperparathyroidism. Treatment should be conservative unless malnutrition becomes a predominant factor.

Immune Dysfunction

A profound effect on host cellular defenses occurs in uremic patients and specific dialysis modalities may have an additional adverse effect on these systems. Numerous immunologic complications may occur in PD related to the use of glucose-based dialysate, the development of peritonitis, and/or inadequate solute clearance [44]. In PD patients with peritonitis, both peripheral (systemic) and local (intraperitoneal) immunity are adversely affected. Polymorphonuclear cells (PMNs), lymphocytes, and macrophages undergo abnormal morphologic changes, and show alterations in cellular function and blunted secretory ability. Furthermore, other host defense cells (e.g. mesothelial cells) may experience similar abnormalities of size and function. These changes have an impact on infection rate, time to resolution, and risks for reoccurrence.

Three interrelated mechanisms combine to recruit leukocytes into the peritoneal cavity during periods of inflammation: direct recruitment, bacterial activation of mesothelium, and peritoneal microphage (PMO): human peritoneal mesothelial cells (HPMC) interaction. During peritonitis there is an influx of leukocytes into the peritoneal cavity. An excessive local production of cytokines by HPMC occurs, but is not prognostic for peritonitis or UF failure. Leukocyte recruitment and transmigration across the peritoneal membrane is dependent on the expression of adhesion molecules – intercellular adhesion molecule-1 (IAM-1) and vascular cell adhesion molecule-1 8VCAM-1 – by HPMC. Secretion of IL-6 and IL-8 proinflammatory cytokines synthesized by mesothelial cells is followed by the activation of the lymphocytes then infiltration and the production of T lymphocyte-derived IL-2 and SIL-2R. This normal series of cellular/humoral events is disrupted in PD.

A number of studies have evaluated the selection and differentiation of lymphocytes in the normal peritoneum. In CAPD, T cells may be functionally abnormal and demon-

strate varying levels of T cell activation. Patients on PD have absolute lymphopenia, however overall cellular immunity may be less depressed on PD than HD, as shown by an increase in T cell population after 12 months on PD. Interestingly, peripheral lymphocytes in CAPD patients suffering frequent bouts of peritonitis were characterized by an increased expression of CD44 variant molecules, normally seen with inflammation and malignant disease. CAPD alters normal peritoneal lymphocytes; neither mRNA transcription of the RAG-1 gene nor CD34 cells are detectable in peritoneal cavity lymphocytes in CAPD patients. Also, thymus-independent T cells are undetectable in the peritoneal lymphocytes from CAPD patients. This results in the loss of CD8α+ subset of natural killer (NK) cells (CD3-, CD8αα+, CD16+ and CD56+), which significantly decreases the peritoneal natural killer activity.

Macrophage effectiveness is limited by several factors in PD patients. Macrophage activation via T lymphocytes and NK cells is adversly affected by these cells' abnormalities. Moreover, the macrophages have increasingly immature bactericidal activity due to their constant flow into the peritoneal cavity from the bone marrow. Finally, these immature cells promote inflammation by their increased cytokine generation ability when stimulated.

Mechanisms involved in the abnormal PMN response in uremia include malnutrition, iron overload, intracellular Ca, low and high molecular weight circulating plasma factors, 1,25 dihydroxy vitamin D levels and the dialysis treatment itself. Porter et al. found CAPD corrected the uremic defect in PMN bacterial killing in 22 patients after 3 months on PD [88]. However, there was no correlation to either urea or creatinine levels. A number of granucyte inhibitory proteins have been isolated from the peritoneal dialysate which include granulocyte inhibitory proteins 1 and 2, degranulation inhibiting proteins 1 and 2, chemotaxis-inhibiting protein, and immunoglobulin light chain kappa and lambda. During acute bacterial peritonitis, monocyte chemotactic protein-1 (MCP-1) is the most important monocyte chemoattractant; whereas IL-8, and human melanoma-growth-stimulating activity (huGRO α) are the major neutrophil-attracting chemokines. It is unclear how inadequate PD might affect the synthesis and decreased excretion of these substances. A modified form of ubiquitin, an inhibitor peptide of chemotactic movement of PMN cells in vitro, has also been isolated from PD dialysate. Some studies have shown that PD therapy may restore PMN intracellular hydrogen peroxide generation to normal levels, possibly due to the removal of low molecular weight toxins in CAPD. While hypoalbuminemic CAPD patients (serum albumin < 3.6 g/dL) had significantly depressed superoxide production volume and velocity, there were no observed differences between patients with and without a history of peritonitis. There does not appear to be a correlation between PMN intracellular killing activity and the rate and type of peritonitis. However, patients with impaired PMN bacterial killing are prone to more severe forms of CAPD peritonitis, and possibly to more frequent infections.

Hypogammaglubulinemia has been reported to develop in infants and children on PD. After IP infusion of immunoglobulin (100 mg/kg) in children with peritonitis, chemotaxis of peripheral blood neutrophils increases significantly. Chemotaxis and luminal-dependent chemiluminescence of both peripheral blood and peritoneal neutrophils of children on CAPD treatment were also enhanced with IP immunoglobulin treatment. Low IP levels of IgG in adults may be associated with an increased risk for peritonitis, although other authors found no correlation

between peritoneal fluid IgG and C3 and the incidence of peritonitis. PD patients with hyperparathyroidism may have a resultant inhibitory effect on B cell function.

Dialysate-induced Immune Defects

Several reports have demonstrated the effect of dialysate on cellular and secretory functions in PD. Dialysis fluid may reduce the host's resistance to infection and potentially can affect the rate or severity of infection risk. Alternate fluid formulations have been or are being developed to lessen this effect. Neutral pH solution buffered with bicarbonate or in combination with lactate or glycyl-glycine may be helpful. Glucose polymer dialysate has been associated with a marked depression of cytokine release. Newer solutions containing bicarbonate or pyruvate, rather than lactate, glucose polymers, glycerol or peptides are being developed to avoid potential toxic effects.

Conventional glucose-based peritoneal dialysate leads to depressed oxygen consumption, chemiluminescence, superoxide production, phagocytosis, bacterial killing, and actin polymerization in neutrophils in vitro [51, 52]. Uremic solutes in PD effluent (e.g. p-cresol) in conjunction with glucose depress normal granulocyte NADPH-oxidase dependent radical species production. Impaired adhesion receptor expression and cell adhesion capacity also exist. Dialysate glucose concentration, low pH, and the presence of lactate ions in racemic mixtures containing both the D- and the L-forms may induce cytotoxicity. Glucose plus lactate-based PD dialysate reduces the capacity of leukocytes for chemotaxis, bacterial killing and production of monokines. Standard dialysate solutions may inhibit mesothelial cell proliferation potentially leading to chronic mesothelial cell damage.

Glucose dialysate may adversely affect superoxide generation by both peripheral and peritoneal phagocytes in CAPD patients. The increased superoxide (O2) generation by peritoneal and circulating phagocytes in CAPD patients is at least partly due to the enhancement of hexose monophosphate shunt activity by increasing glucose metabolism and the increased O2 generation might be involved in long-term complications of CAPD.

There has been an individual case of reactivation of SLE after transfer to PD.

Hospitalization Risks and Complication Prevention

Despite increases in the average age of incident ESRD patients from 1996 to 1988 (57 vs. 61 years), the percent of diabetic patients on dialysis (30 – 43%), and the number of co-morbid risk factors, the US dialysis mortality rate has declined to 17%. Hospitalization rates and length of stay have declined but are still unacceptably high. Renal failure patients are 10 times more likely to be hospitalized and on average, hospitalization lasts one day longer compared to non renal failure patients. A national hospital survey identified 348,962 hospitalizations for patients with renal failure in 1991. As the numbers of patients with ESRD on dialysis increase, hospitalizations continue to escalate. Inpatient health resource utilization accounted for 44% of the total cost for the Medicare ESRD program in this study [104]. In 1991 hospital days for ESRD beneficiaries numbered 3.1 million and the total ESRD program expenditures were $2.7 billion.

Haback et al. [37] compared hospitalization for patients treated with PD vs. HD using data

from the USRDS 1993 annual report. Average hospital admission rates/patient-year at risk for PD patients were 14% higher than for those treated with HD after adjustment for race, age, gender and cause of ESRD. Furthermore, diabetic patients treated with PD had a 12% higher admission rate/patient-year at risk than did diabetics treated with HD. Younger diabetic patients (20 – 40 years old) had similar admission rates, whereas patients > 45 years old had an 18% higher admission rate than did diabetics treated with HD. Nondiabetic PD patients had 15% higher admission rates than did nondiabetic HD patients. While this study did not factor in patient co-morbidities from the dialysis modality, the underlying message is that patients with suboptimal clearances despite dialysis have an increased risk for hospitalization and a longer hospital stay. Ten percent of hospitalizations in dialysis patients had a length of stay > 23 days. Children < 5 years old had higher dialysis-related hospitalization rates and durations on PD than HD. Every center should have the ability to track complication rates, at the very least peritonitis and CESI, both in the outpatient and hospital settings.

Providing adequate dialysis is the key not only to survival, but also to avoiding increased hospitalization rates. A recent reexamination of the USRDS data has demonstrated a stable rate of death comparing HD to PD over the last several years, and in some studies, an improved survival rate on PD compared to HD during the first 2 years of therapy. Therefore, complication rates can be decreased by providing adequate dialysis and early preventive intervention in patients who may be at increased risk for complications. Specific risk factors associated with higher rates of hospitalization utilization/year of patient risk include increasing age, decreased activity level defined by a Karnovsky score, DM as a cause of ESRD, and decreased serum albumin level; whereby the strongest predictor of hospitalization rates was low serum albumin level. Every effort needs to be made to modify these and other risk factors.

Diabetic patients had a 40% higher admission rate/patient-year at risk than did nondiabetics. Admission rates were higher for males, whites and PD patients in the Haback study. Excess admission rates among diabetics compared to nondiabetics increased with patient age. PD patients needed 4.6 hospital days/year at risk more than HD patients, with the length of stay averaging 11.74 and 10.58 days/admission for dialysis patients treated with PD and HD, respectively. These findings are modifiable, considering the percent of US patients who require changes in their prescription dialysis to meet target clearances.

Because admission to the hospital significantly increases overall disease morbidity and may result in subsequent increased deaths, avoiding admissions and emergency room visits is of critical importance in dialysis care. In reviewing total hospital admissions by diagnosis [diagnosis-related group (DRG) category for 1993 – 1995], the top 6 systems were circulatory, renal, GI, infection, respiratory and nutrition. Those specifically related to PD include congestive heart failure (CHF), circulatory system, septicemia, nutritional and miscellaneous metabolic disorders, pneumonia, and esophagitis. Understanding these risk factors for hospitalization in ESRD can result in developing interventional strategies to decrease morbidity.

CHF admissions may result from a mismatch between prescription and membrane transport type, often occuring shortly after the initiation of PD. Patients with cardiomyopathy, altered cardiac output, edema at the time of dialysis initiation, and uncontrolled DM may be at increased risk for CHF admissions. Individuals with significant ventricular arrhythmias may also be at increased

risk for compromised cardiac output. Thus, it is essential to optimize diabetic control ($HbA_1C < 8$), achieve euvolemia, and optimize nutrition. Prompt diagnosis of peritonitis with aggressive treatment and identification of limb cellulitis in diabetics is crucial. Nutrition disorders should be vigorously addressed in patients with serum albumin < 3 g/dL. Pneumococcal and influenza vaccinations and early treatment of pulmonary infections may avoid simple pneumonia admissions. Esophagitis may occur in DM, HIV or other immunocompromised patients on PD. Endoscopy may be warranted in patients with persistent nausea, vomiting and poor nutritional status.

On entering PD programs, patients' risk status should be evaluated and pro-active measures taken to avoid hospitalizations. Knowing the level of predialysis glycemic control, an independent predictor of clinical outcome in type II DM, prior to dialysis will aid in risk categorization. Major risk factors in PD include: sepsis, poor nutrition, respiratory dysfunction, esophagitis, peritonitis, uncontrolled DM, LVH, CHF, arrhythmias, CAD, peripheral vascular disease with ischemia, and cellulitis. HIV-infected patients have higher rates of peritonitis. While the risk of nasal *S. aureus* carriage remains controversial, those carrier states identified should be treated (see above). Standardizing treatment approaches and developing care guidelines will help decrease complications warranting admission. Hospitalizations have a negative impact on achieving quality indicator goals; utilizing best demonstrated practices and tracking of patients at higher risk are essential.

By the year 2000, 45 – 55% of all patients on ESRD will have DM as their renal failure etiology. Currently, the major reasons for poor outcome are cardiovascular disease in 56%, cachexia in 18%, and infection in 11%. Impaired vision, decreased manual dexterity, frequent presence of bowel diverticulae, poor hygiene, socioeconomic level, need for caretaker, and impaired immunologic defense all tend to increase with age for patients on PD. The 5-year survival for diabetic patients on dialysis is approximately 18 – 28%. Almost half of all diabetic ESRD patients do not survive 2 years. Peritonitis rates are significantly higher in diabetics vs. nondiabetics. Diabetics have an increased complication risk and a higher hospital admission rate due to coexistent disease. Managing risk is essential to improving this poor outlook.

The drop-out rate from infection is higher in younger patients, whereas elderly patients' increased morbidity and mortality are mainly associated with complications not related to CAPD. Hospitalizations are significantly longer in the elderly, and the risk for malnutrition and decreased muscle mass is higher. There is no difference in peritoneal function, UF rates, peritoneal transport, or clearance goals in young and elderly patients. By the year 2000, 65% of all ESRD patients will be older than 65 years of age. Their special needs will have to be considered: malnutrition, bowel dysfunction, increased chronic diverticulae, DM, neoplasia, peripheral vascular disease, and variable mental alertness which obviously affects self-care.

African-American patients are less likely to be hospitalized, less likely to choose PD as initial therapy (11.6% vs. 29.3%) and are less likely to change dialysis modalities once on HD. African-Americans have an increased susceptibility to *S. aureus* and *S. epidermidis* infections, which should be stressed in preventive strategy initiatives.

Increased peritoneal membrane transport is associated with decreased patient and technique survival for CAPD patients. High-transport CAPD patients have worse nutritional status than those with low-transport characteristics. Potentially, this may be due to

Table 9. In-patient PD Complications Settings[1]

Clinical Settings	Associated Complication	Dialysis Prescription Modifications
Congestive heart failure	– Resistant hypervolemia[2] – Increased a-$A_0$2 gradient – Intubation	– Utilize short dwell times (20 to 60 minutes) – Achieve dry weight ≤ 48 hours – Ultrafiltration (UF) 4% body weight (8 to 10 hours)
Coronary artery bypass grafting	– Reintubation – Sternal infection/osteomyelitis[3] – Hypokalemia – Malnutrition[6]	– Aggressive solute/water removal[4] – Usually automated PD ≥12 hours/day – Achieve preoperative weight
Cellulitis	– Poor infection response – Uncontrolled blood sugar[5] – Persistent limb edema – Amputation	– UF to achieve euvolemia – Remove ALL edema
Aortic-femoral revascularization	– Wound dehiscence, “localized dialysate leak” – Postoperative wound infection[7] – Malnutrition – Resistant edema	– Avoid edema/increase UF – Decrease dwell volume perioperatively – Avoid dialysate “seepage” into wound – Optimize solute clearance
Lower extremity amputation	– Stump dehiscence – Postoperative wound infection – Resistant edema	– BUN/albumin ≤ 17 – optimal fluid removal
Pneumonia	– Resistant infection[6] – Intubation – Sepsis – Interstitial edema – Respiratory failure – Increased A-a0_2 gradient	– Control volume to solute ratio

[1]Design prescription to optimize solute/water removal [vary dwell time days 1 to 3 (i.e., 60, 90, 120 minutes) to establish PET category if previously unknown]. [2]Increased pulmonary capillary wedge pressure (PCWP) > 16 mm water. [3]Avoid chest wall edema to optimize suture-line closures. [4]Achieve BUN/Alb ≤ 17. [5]Optimize blood sugar control, extend perioperative antibiotic prophylaxis. [6]Serum albumin < 3 gm/dL (protein supplements, entero feedings, total parenteral nutrition, megastrol acetate 40 Ä 400 mg daily). [7]Utilize IV antibiotics, aggressive pulmonary toilet.

increased losses of protein in the dialysate and volume expansion attributable to decreased UF. High-transport patients have lower serum albumin concentrations even at one month into CAPD and the serum albumin remains lower at 2 years on CAPD.

A number of inpatient clinical settings further increase the risk for PD-related complications (Table 9): CHF, cellulitis or sepsis, acute MI, ischemic heart disease or unstable angina. Recovery following laparoscopic cholecystectomy, coronary revascularization,

amputation, heart valve surgery, recent extubation are all considered as compounding high risk transition periods for patients on PD. Specific parameters should be followed in these patients, and glucose control, dialysis prescriptions, and nutritional support adjusted to meet the ongoing demands. It is essential that the clinician anticipate problems and structure care to prevent problems from developing in high-risk clinical settings.

Patients admitted to the hospital should have special attention given to effective solute removal and volume control. These patients may need significantly longer times on automated therapy, particularly if they are hypercatabolic. Ideally, the BUN to albumin ratio should decrease ≤ 17 through aggressive dialysis. Patients with serum albumin levels < 3 g/dL should undergo enteral feedings or aggressive oral supplementation. Patients are not compliant in taking daily protein supplements in the hospital for a multitude of reasons and therefore, enteral feeding is preferable. Total parenteral nutrition may be utilized if the GI tract is not functional. Volume control is especially important in patients postoperatively, especially those who have limb surgery. Edema in a limb or in the inguinal area may increase the risk for wound dehiscence and secondary bacterial infection. Aggressive UF should occur to decrease peripheral edema and maintain effective respiratory status. Dialysis patients (especially diabetics) have a significantly higher rate of reintubation than standard individuals.

Impaired pulmonary oxygenation in diabetic patients undergoing coronary artery bypass grafting (CABG) can be a worrisome problem because of various structural and/or functional abnormalities of the lung in diabetics [96]. Pulmonary diffusion capacity and pulmonary capillary blood volume are compromised in patients with diabetes perioperatively. The pulmonary capillary wedge pressure is the variable that has the greatest effect on pulmonary function in the nondiabetic group. Low FIO_2 and high central venous pressure are indicators of pulmonary compromise. The alveolar arterial oxygen (A-aPO_2) gradient and respiratory index are more abnormal postoperatively in diabetics than nondiabetics at similar volume levels. Therefore, smaller elevations above normal in wedge pressure or central venous pressure above normal in a diabetic patient may significantly increase the risk for pulmonary failure and need for reintubation. Effective UF in maintaining low capillary wedge pressure is essential to optimizing the A-aPO_2 gradient.

Impaired ventilatory response to carbon dioxide in CRF patients has grave implications in the intensive care unit. Optimally-dialyzed PD patients demonstrate definite improvement in the ventilatory response to CO_2. CRF patients have a poorly-responsive ventilatory control system, which makes them more difficult to wean from mechanical ventilation, making them even more vulnerable to disturbances in blood gas homeostasis and subsequent respiratory arrest. Reintubation adds significant risk to overall mortality perioperatively.

Summary

ESRD patients treated with PD have the potential to develop serious complications across a broad spectrum of organ systems. While many complications are directly related to dialysis itself, a number are due to the uremic state unaffected by the specific dialytic modality. Because of the overall risk for CRF patients on dialysis to undergo hospitalization, steps taken to avoid admission are

crucial. High-risk patient groups have been identified and warrant closer follow up in the outpatient setting. Specific medical problems which increase the risk of hospitalization should be aggressively treated. Patients admitted either emergently or electively should be closely followed in the hospital, and aggressive dialysis for solute and water removal implemented along with supplemental nutritional support if indicated. Preventive strategies both in the outpatient and inpatient arenas can significantly decrease morbidity and optimize overall long-term survival.

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