Peritoneal Dialysis–Associated Peritonitis with Simultaneous Exit-Site Infection

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Summary
With the implementation of best demonstrated clinical practices, peritonitis has become an infrequent complication of peritoneal dialysis in many centers around the world. Yet the gains in reduction in risk of peritonitis are not uniform. Most episodes of peritonitis do not require hospitalization and it is possible to achieve cure rates of 70%–80%. Some circumstances, however, necessitate the removal of the peritoneal dialysis catheter. These include patients with inadequate response to antimicrobial therapy, those with fungal peritonitis, or those with *Staphylococcus aureus* or *Pseudomonas* peritonitis with coexisting exit-site infection with the same organism. If the peritoneal dialysis catheter is removed in the presence of active intraperitoneal infection, replacement of the peritoneal dialysis catheter should be deferred by 2–4 weeks. However, simultaneous removal and replacement is possible in selected circumstances such as in patients with *S. aureus* or *Pseudomonas* peritonitis who also have exit-site infection with the same organism, after the intraperitoneal infection has responded to antibiotic therapy.

Introduction
A 58-year-old woman with type 2 diabetes, diabetic nephropathy, and ESRD has been undergoing treatment with automated peritoneal dialysis for the last 2 years (four exchanges overnight using a cycler over 9 hours with a single-day dwell with icodextrin), and she presented to the emergency department with severe abdominal pain and cloudy dialysate. She had been in her usual state of health until about 12 hours ago, when she first developed abdominal pain. When she performed her routinely scheduled peritoneal dialysis exchange, she noticed that the effluent was cloudy. Since then, the pain has progressively increased in severity such that she has been unable to perform her peritoneal dialysis at home. The pain is continuous and is present diffusely all over the abdomen, but does not radiate either to the back or to the shoulder. She does not have any associated chills, fever, nausea, or vomiting, but has not been able to eat anything since then. She does not have any pets or toddlers at home and does not recall any break in sterility in performing the peritoneal dialysis exchanges. She has been cleaning her peritoneal dialysis catheter exit site daily, first with soap and water, and then with chlortetraxine before covering it with a gauze. She had not noticed any erythema or discharge at the exit site up until the time of presentation.

Her past medical history was significant for type 2 diabetes, diabetic retinopathy, hypertension, and hyperlipidemia, as well as a history of cholecystectomy 5 years earlier. A polyurethane peritoneal dialysis catheter had been placed with the assistance of a laparoscope 2 years ago. Up until now, she had never had either an exit-site infection or peritonitis. She reported no current tobacco, drug, or alcohol use. She was married and lived with her husband. Her current medications included benazepril, atenolol, simvastatin, aspirin, sevelamer, calcitriol, and weekly erythropoietin.

On examination, she appeared extremely uncomfortable because of pain. Her temperature was 36.5°C, and her pulse rate was 105/min, BP was 153/84 mmHg, and respiratory rate was 24/min. She weighed 71 kg, she had no jugular venous distension or lower extremity edema, and her cardiopulmonary examination was unremarkable. Her abdomen was diffusely tender, she had rebound tenderness, and the bowel sounds were present but sluggish. Inspection of the exit site showed circumferential erythema along with purulent drainage at the 3–o’clock position. Palpation of the catheter tunnel was equally painful as the rest of the abdomen.

Laboratory data showed a blood white blood cell count of 7200 cells/mm³ (70% neutrophils, no bands), hemoglobin of 11.7 g/dl, and a platelet count of 231,000/mm³. The serum chemistry results were as follows: 136 mEq/L sodium, 3.9 mEq/L potassium, 110 mEq/L chloride, 23 mEq/L bicarbonate, 58 mg/dl BUN, 6.3 mg/dl serum creatinine, 248 mg/dl glucose, 8.1 mg/dl calcium, 5.9 mg/dl phosphorus, and 3.2 g/dl albumin (bromcresol purple). The serum amylase and lipase were 80 and 45 U/L, respectively.

Given her inability to perform peritoneal dialysis exchanges at home, and to eat or drink at home, a decision was made to hospitalize the patient. Because she did not have intraperitoneal dialysate at the time of presentation, effluent was not available immediately for testing. In the emergency room, dialysate was instilled into the abdomen, drained after 2 hours, and
sent for obtaining effluent white blood cell count, Gram stain, and culture. Pending these results, empirical treatment was started with intraperitoneal cefazolin (500 mg/L loading followed by 125 mg/L in each subsequent exchange) and ceftazidime (500 mg/L followed by 125 mg/L in each subsequent exchange) along with nystatin swish and swallow thrice daily for prophylaxis against fungal superinfection.

Case Discussion
This is a 58-year-old woman treated with peritoneal dialysis who presented to the emergency room with severe, disabling abdominal pain and cloudy dialysate for 12 hours. In addition, she has erythema and purulent drainage at the exit site. The clinical presentation is consistent with a diagnosis of peritoneal dialysis–associated peritonitis and the coexistence of exit-site infection raises concern for catheter-related infection. Staphylococcus aureus and Pseudomonas are the two organisms most commonly associated with catheter infection–associated peritonitis in patients treated with peritoneal dialysis. Let us review the clinical approach to this patient (Figure 1).

Diagnostic Considerations and Approach
Generally, a diagnosis of peritonitis in patients treated with peritoneal dialysis can be made if two of the following three criteria are met: abdominal pain, dialysate effluent total white blood cell count >100/µL (>50% PMNs), or positive Gram stain and/or culture (1). However, at the time of initial presentation of the patient and clinical decision making, the results of neither the effluent white blood cell count nor the microbiologic data are available like in this patient. The overwhelming majority of patients treated with peritoneal dialysis with abdominal pain and cloudy dialysate have infectious peritonitis, and it is imperative not to delay initiation of antimicrobial therapy in such cases. Thus, it is prudent to make a presumptive diagnosis of infectious peritonitis in this patient and begin empirical treatment with intraperitoneal antibiotics without waiting for the results of the dialysate effluent cell counts, Gram stain, or culture (1). Nevertheless, clinical conditions like pancreatitis, chemical peritonitis, peritoneal eosinophilia, or encapsulating peritoneal sclerosis can present with the same constellation of symptoms (1,2). As relevant to this patient, an outbreak of chemical peritonitis was described in patients treated with icodextrin in Europe in 2001–2002 (3,4). This was traced to the presence of significant concentrations of peptidoglycan from corn-starch, the same substrate from which icodextrin is derived (5). The manufacturing process has since been modified such that commercially available icodextrin today has no detectable peptidoglycan. Although chemical peritonitis can still occur with the commercial preparations.

Figure 1. | Algorithm for the management of peritoneal-dialysis associated peritonitis. PD, peritoneal dialysis.
of icodextrin available today, it is extremely infrequent (6). Thus, it would be inappropriate to attribute the patient’s symptoms to icodextrin-associated chemical peritonitis. Instead, she should be assumed to have infectious peritonitis and treated empirically as such. Finally, chylorperitonaeum is a rare condition in which the peritoneal effluent appears milky, which may appear to be pus to the inexperienced eye (1,7). However, patients with chylorperitonaeum generally do not have abdominal pain and the absence of intraperitoneal inflammation can be confirmed by a measurement of the total white blood cell count in the effluent.

Before the instillation of intraperitoneal antibiotics, a sample of the peritoneal dialysis effluent should be sent for white blood cell count, Gram stain, and culture. Samples obtained from patients with no intra-abdominal dialysate can have a falsel y high total white blood cell count (1). It is not infrequent for patients with severe abdominal pain to stop performing peritoneal dialysis exchanges as done by our present patient. In such circumstances, it is important to instill fresh dialysate, allow it to dwell for 1–2 hours and then send a sample for testing (1). Because intraperitoneal dialysate is periodically drained with instillation of fresh dialysate several times a day in patients treated with peritoneal dialysis, the threshold total white blood cell count (>100/μl) for the diagnosis of peritonitis is considerably lower than what is used for the diagnosis of spontaneous bacterial peritonitis in patients with chronic liver disease (>500/μl) (1). In patients with marginal elevation of total effluent white blood cell counts, a diagnosis of infectious peritonitis should be considered if >50% of the cells are polymorphonuclear white blood cells (1).

Even though Gram stain is routinely requested to be performed in such circumstances, it is virtually never positive in patients with bacterial peritoneal dialysis–related peritonitis (1). However, yeast is frequently detectable on Gram stain in patients with fungal peritonitis (1). This allows for a rapid diagnosis of a serious condition that generally necessitates emergent removal of the peritoneal dialysis catheter. Hence, it is prudent to request Gram stain of the peritoneal dialysate effluent in our patient. Inoculating a large volume of dialysate increases the likelihood of obtaining a positive effluent culture and should be done in this case (1). Peritoneal dialysis–related peritonitis is rarely, if ever, associated with bacteremia (1). Because there are no signs of systemic infection in this patient, it is not necessary to obtain blood cultures in this patient.

Inspection of the peritoneal dialysis catheter exit site is critical in the evaluation of patients undergoing peritoneal dialysis, particularly when they present with peritonitis. Although erythema at the exit site can be a result of other causes such as trauma, the additional presence of purulent drainage in this patient establishes the presence of coexisting exit-site infection (1,8). If the bacterial isolate from the peritoneal dialysis catheter exit site is the same as the one from the dialysate effluent, the patient should be presumed to have catheter-related peritonitis (1). In such cases, complete cure generally necessitates the removal of the peritoneal dialysis catheter (9). Because the results of the exit-site culture will change the management plan for this patient, it is important to send a swab of the purulent drainage at the exit site for culture. The risk for exit-site infection in this patient would have been lower with the prophylactic application of antibiotics at the exit site (mupirocin or gentamicin) (10–12). However, the alcohol base used in antibiotic ointments can damage the polyurethane catheter (13). The antibiotic creams are an oil emulsion; even though they are less toxic, antibiotic creams can also damage peritoneal dialysis catheters. Thus, the topical application of antibiotics at the catheter exit site is contraindicated in this patient. An alternative strategy, demonstrably effective in clinical trials in reducing Staphylococcus infections, would have been to apply mupirocin to the nares (14). The acceptance and adherence of applying antibiotics to the nares is low and was not used in this patient, putting her at higher risk for the development of exit-site infection.

**Principles of Initial Management**

The goals of managing the patient at this time are two-fold: antimicrobial therapy and relief of pain. In a large survey of almost 9000 episodes of peritonitis in 61 facilities from North America, almost 60% of the isolates were Gram-positive and 20% were Gram-negative organisms (15). Of the remaining 20% of peritonitis episodes, most were culture negative, with fewer being fungal or polymicrobial. It is important then to ensure that the empirical antibiotic regimen provides adequate activity against both Gram-positive and Gram-negative organisms. The selection of antibiotics should be dictated by the sensitivity patterns of the isolates from each dialysis facility (1). Cefazolin and vancomycin are the two most commonly used antibiotics with activity against Gram-positive organisms and ceftazidime and aminoglycosides for Gram-negative organisms (1). Cefazolin is generally preferable over vancomycin because of concern about the emergence of organisms resistant to the latter. The concern that use of aminoglycosides may accelerate the decline of residual renal function in patients treated with peritoneal dialysis has not been borne out in a randomized controlled clinical trial (16,17). Nevertheless, ceftazidime is preferable over aminoglycosides because of risk of ototoxicity with the latter. This forms the rationale for the selection of cefazolin and ceftazidime for the empirical treatment of peritonitis in this patient. In lieu of combination therapy, monotherapy with carbapenems or cefepime has been demonstrated to be effective for the treatment of peritoneal dialysis–related peritonitis and may be used as alternatives (18,19). In contrast, monotherapy with quinolones leads to emergence of resistant organisms and should not be used (20).

Antibiotics administered intraperitoneally provide high concentrations locally that are sustained for the length of the dwell, and this is the preferred approach (1). The high concentrations of the drug obtained locally are particularly important in cases in which the infection is caused by organisms with an intermediate level of sensitivity to antibiotics, particularly coagulase-negative staphylococci. If logistical considerations preclude the immediate intraperitoneal administration of the antibiotics, it is preferable to administer the antibiotics intravenously rather than delay treatment. However, the route of administration should be switched to intraperitoneal as soon as possible.
The treatment regimen is defined as continuous or intermittent based upon the frequency of administration (1). When the antibiotics are added to every dialysate bag used by the patient, the regimen is defined as continuous. In contrast, a regimen is considered intermittent if the antibiotics are added only to some but not all of the bags. Whether continuous or intermittent dosing regimens are used depends upon the antibiotics and dialysis facility. Thus, vancomycin (dosed once every 3–5 days, depending upon residual renal function) and aminoglycosides (dosed once daily) can be safely administered intermittently (1). There is far less certainty about how best to dose cephalosporins. There are no clinical trials that have compared continuous versus intermittent dosing regimens for cephalosporins for peritoneal dialysis–related peritonitis. Pharmacokinetic studies performed in peritoneal dialysis patients in the absence of active infection suggest that at 24 hours, intermittent dosing regimens can provide intraperitoneal concentrations that are higher than the minimum inhibitory concentration for sensitive isolates (21–23). This suggests that one single, large dose daily may provide therapeutic efficacy and is substantially more convenient for patients. However, the clearance of the drugs is significantly increased in the presence of peritonitis, raising concern that there may be significant periods of time when the drug concentrations may become subtherapeutic (1). The concern of subtherapeutic drug concentrations is particularly greater in patients with significant residual renal function. Thus, a continuous dosing regimen—adding a smaller dose of the drug in each bag—is a conservative approach for the treatment of peritoneal dialysis–related peritonitis and can be readily applied while the patient is maintained on cycler therapy (24). If antibiotics are dosed intermittently (cephasporins, vancomycin, or aminoglycosides), it is important to allow the dialysate with the drug to dwell for at least 6 hours to ensure sufficient systemic absorption (1). When using intermittent dosing regimens in patients treated with automated peritoneal dialysis, antibiotics should be added to the long-day dwell (1).

Pain is a potentially disabling symptom of peritoneal dialysis–related peritonitis (25). Effective treatment of the intraperitoneal infection with antibiotics is the best analgesic. However, it takes 24–48 hours of antibiotic treatment to reduce the pain and additional interventions may be needed in the interim. The acidic pH of the conventional peritoneal dialysis solutions can worsen the pain associated with peritonitis. Adding a small volume of sodium bicarbonate (10–15 ml of 5% sodium bicarbonate) can produce dramatic alleviation of pain in many patients. If this is not effective, narcotic analgesics may be used along with an effective bowel regimen to minimize constipation.

**Follow-Up**

Four hours after hospitalization, the results of the peritoneal dialysate effluent showed a total white blood cell count of 3600/μL, 70% of which were PMNs. The Gram stain was negative. Treatment with automated peritoneal dialysis was continued; for the first 24 hours, the patient required the addition of sodium bicarbonate to the dialysate for the relief of the pain. The next day, the culture results of both the exit site and peritoneal dialysate returned positive for methicillin-sensitive *S. aureus*. At this time, cefazidime was discontinued and monotherapy with cefazolin was continued.

Over the next 4 days, the trend for the total white blood cell count was 1900, 700, 300, and 120/μL. Her repeat peritoneal dialysate effluent cultures were negative. She was discharged with plans to continue treatment with intraperitoneal cefazolin for a total of 3 weeks. Because *S. aureus* was isolated from both the exit site and the peritoneal fluid and the intraperitoneal infection had resolved with antibiotics, a decision was made to perform simultaneous removal and replacement of the peritoneal dialysis catheter after 3 weeks of antibiotic therapy.

**Simultaneous Removal and Replacement**

In this patient, the intraperitoneal infection cleared rapidly with antibiotic therapy alone. However, the isolation of the same organism from the exit site as well as dialysate effluent is highly suggest that this patient has a concomitant tunnel infection and will be at high risk of relapse upon discontinuation of antibiotic therapy. This case thus represents an unusual circumstance in which it is prudent to remove the peritoneal dialysis catheter despite resolution of the intraperitoneal infection. Because the dialysate effluent is sterile, it is feasible to place a new peritoneal dialysis catheter with an exit site fashioned on the contralateral side at the same time when the old catheter is removed—the so-called “simultaneous removal and replacement” or the peritoneal dialysis catheter (26). A significant proportion of published data on simultaneous removal and replacement of the peritoneal dialysis catheter pertain to *Pseudomonas* catheter infections (27); the data on this approach in patients with *Staphylococcus* infections are more limited. Thus, the application of this approach in this patient reflected the clinical judgment that in the setting of rapid clearance of the intraperitoneal infection the risk of relapse of catheter infection with simultaneous removal and replacement was lower than the morbidity of placing a central venous catheter for temporary in-center hemodialysis.

**Final Diagnosis.** *S. aureus* exit-site infection and peritonitis.

**Dr. Singh.** Other than the risk of infection of the new catheter, are there other important issues to consider in patients who undergo a simultaneous removal and replacement of the peritoneal dialysis catheter?

**Dr. Mehrotra.** Considerable care needs to be exercised in managing the peritoneal dialysis prescription in such a patient. The tunnel track of the new peritoneal dialysis catheter takes about 2 weeks to heal completely (28). The increase in intraperitoneal pressure associated with the instillation of 2.0–2.5 L of dialysate used in conventional peritoneal dialysis prescriptions can result in leakage of the dialysate with its attendant complications. In patients with significant residual renal function, it is generally safe to suspend all dialysis treatments for 2 weeks while imposing strict dietary sodium, potassium, and water restriction under close clinical supervision. This is not feasible in patients without significant residual renal function and low-volume supine peritoneal dialysis should be performed in such cases. This is readily accomplished with the use of a cycler with 1.0 L instillations for 8–10 exchanges overnight while the patient is supine with
no intraperitoneal fluid during the daytime (28). Such a prescription will generally be unable to meet the adequacy targets for small solute clearances but is sufficient to maintain general health and, most importantly, obviates the morbidity from the use of central venous catheters.

**Dr. Singh.** Under what other circumstances can we consider simultaneous removal and replacement of the peritoneal dialysis catheter?

**Dr. Mehotra.** Simultaneous removal and replacement is also a useful approach in patients with refractory exit-site infection or in those with relapsing or repeat peritonitis. Relapse is defined as intraperitoneal infection with the same organism 4 weeks after cessation of antibiotic therapy (1). A simultaneous removal and replacement should be done in patients with relapsing or repeat peritonitis only if the intraperitoneal infection has resolved while continuing antibiotic therapy for a few days after the catheter exchange.

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**References**


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