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Peritonitis in Peritoneal Dialysis

Sohail Abdul Salim and Tibor Fülöp

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Abstract

Peritoneal dialysis (PD) involves solute and water transport across a semipermeable membrane that separates fluid compartments. Peritonitis is a serious complication of peritoneal dialysis that results in considerable morbidity and health care costs. It also significantly distorts the normal anatomy of the peritoneal membrane causing transient and long-term adverse events. Bacterial as well as fungal organisms can cause peritonitis and sometimes cultures can be negative. As much as 5–16% of deaths occur in PD even though the rate of infections has been in decline in last few years. Below we will be reviewing risk factors, host's immune defenses, prevention, diagnosis and evidence-based treatment, types of peritonitis with a role of prophylactic antibiotics for PD peritonitis.

Keywords: bacteria, abdominal pain, leukocytosis, treatment, antibiotics

1. Introduction

Peritoneal dialysis is one of two principal modalities for renal replacement therapy and has been utilized extensively in many countries including Hong-Kong, Mexico, Thailand, Canada, the Netherlands, Australia and Denmark. One of the commonest complications of peritoneal dialysis is peritonitis, which leads to increased health care costs, hospitalizations, catheter removal, malnutrition and peritoneal membrane damage. Survival on PD continues to improve in the United States, with overall survival as good as for similar patients during in-center hemodialysis (HD). Nonetheless, approximately 20% of patients undergo a modality switch to HD during their first year on PD due to modality or access-related infections. Repeated episodes of bacterial peritonitis are a major factor leading to the loss of peritoneal function and resulting in failure of PD [1, 2]. PD peritonitis seldom evolves into systemic bacteremia or fungemia and the infection remains as a rule confined to the peritoneal cavity. With increased

peritoneal permeability during peritonitis, a reduction in ultrafiltration occurs, which would lead to fluid accumulation and potential symptomatic volume overload.

2. Relative immunosuppression in end-stage renal disease

Peritoneal leucocytes are predominant players in combating bacteria in the peritoneal cavity. Most dialysate solutions have an unphysiological pH of 5, which might inhibit the phagocytic ability of these leucocytes. End-stage renal disease (ESRD) impairs both innate and adaptive immune responses. Decreased endocytosis and impaired maturation of monocytes and dendritic cells are demonstrated in the uremic state, contributing to an increased susceptibility to infections [3, 4]. Impaired maturation of thymic lymphocytes and impaired functions of toll-like receptors (which provide protection against infections) also increase the susceptibility to infections.

3. Strategies for prevention of peritonitis

Peritonitis with automated peritoneal dialysis (APD) and continuous ambulatory peritoneal dialysis (CAPD) are not different. All PD programs in the United States monitor the incidence of peritonitis (rates should be no higher than 0.5 episodes per year), which helps programs target interventions when rates go high. The Baxter database of 35 US centers reports 3111 episodes of peritonitis with an overall peritonitis rate of 1 per 33 patient months, while the overall exit site infection (ESI) rate is 1 per 65 patient months. Reported causes of peritonitis include contamination during treatments, untreated PD catheter tunnel or exit point infections, transmural migration of organisms from the gut due to diverticulitis, systemic infections and procedural instrumentation (gynecologic, dental or post-colonoscopy). Touch contamination is the most common source followed by ESI and tunneled catheter infections. Jassal reported an association between a treated ESI and subsequent PD peritonitis [5]. One of the earliest multi-center randomized clinical trials comparing the Y connector disinfectant system to standard systems showed superiority and decreased infections with Y connectors using “flush before fill” techniques [6]. The practice has become widespread since. Appropriate interventions including educating and teaching patients’ strict aseptic precautions (including hand hygiene) during exchanges along with intensive retraining and reinforcement of sterile techniques might have led to a decrease in infections.

In the last 2 decades we have realized that exit site and tunneled infections contribute extensively to peritonitis risk in the days immediately following the diagnosis. Treatment of an exit site infections are especially critical as the peritonitis risk is increased >10-fold in the first 15 days with a progressive decrease but continuous presence up to 2–3 months [5]. These observations resulted in the practice of daily topical application for prophylactic antibiotic (mupirocin or gentamicin) creams or ointments to the catheter exit sites and prompt treatment of ESI worldwide. A double-blind randomized trial showed that the daily application of gentamicin cream on the exit site resulted in a 57%-reduction in ESI and a 35%-reduction in peritonitis compared with mupirocin. Gentamycin, a bactericide, also prevented infections with

Social/environmental

- Smoking
- Living distantly from PD unit
- Pets

Medical

- Obesity
- Depression
- Hypokalemia
- Hypoalbuminemia
- Absence of vitamin D supplementation
- Invasive interventions (e.g. colonoscopy)

Dialysis-related

- Prior hemodialysis
- PD against patient's choice
- Training
- Bioincompatible fluids
- Wet contamination

Infection-related

- Nasal *Staphylococcus aureus* carrier status
 - Previous exit site infection
-

Adapted from Cho [19] and ISPD 2016 guidelines [20].

Table 1. Modifiable risk factors of peritonitis.

Staphylococcus aureus and *Pseudomonas aeruginosa* [7]. At least 3 trials have shown that topical exit site disinfection with povidone-iodine did not reduce the risk of peritonitis compared to soap and water or no treatment [8, 9]. Randomized controlled trial (RCT) of mupirocin to a “triple-antibiotic” combination (bacitracin, gramicidin and polymyxin B) showed non-superiority to mupirocin and concern for fungal colonization of exit site with triple-antibiotic use. Further, exit site trauma should be treated with antibiotic prophylaxis. High levels of soluble C5b-9 in the dialysate predict poor prognosis during peritonitis [10]. Antifungal prophylaxis with oral fluconazole (200 mg orally on day one, then 100 mg/day for 1 week after completion of treatment) or nystatin (500,000 IU orally three times a day while on antibiotics) can be considered with concurrent antibiotic use, while treating peritonitis to prevent fungal peritonitis. There is uncertainty regarding fluconazole for prophylaxis against fungal peritonitis but one RCT supported the use of nystatin [11].

Antimicrobial actions of peritoneal macrophages are enhanced by both calcium and vitamin D. Kerschbaum reported that calcitriol decreased the risk of peritonitis and improved survival [12]. Even though there were initial reports of low peritonitis rates with low glucose-degradation-product (GDP) solutions, a subsequent meta-analysis of 6 randomized controlled trials concludes uncertainty at this time [13, 14]. Gastroenteritis and hypokalemia

have been linked to peritonitis risk, though there is no evidence that treating these would decrease said risk. **Table 1** lists modifiable risk factors for peritonitis. For hypokalemia management and prophylaxis, potassium-sparing diuretics are effective even in PD patients [15–17]. Most nephrologists agree on the importance of avoiding constipation to prevent peritonitis and monitoring peritonitis rates and trends in their programs with intensive retraining in patients with frequent episodes of peritonitis. The International Society of Peritoneal Dialysis (ISPD) recommends prophylactic systemic antibiotics immediately prior to catheter insertion on the basis of 4 RCT. Placement of PD catheters with a downward-facing exit site decreases risk. Nevertheless, the 2017 ISPD guidelines concluded that none of the catheter placement techniques are superior in the prevention of any catheter-related infection [18]. The use of topical mupirocin in patients with colonization of nares is recommended before PD catheter insertion. The role of prophylactic antibiotics in preventing peritonitis is discussed in detail below.

4. Role of prophylactic antibiotics prior to procedures

Invasive interventional procedures like colonoscopy, hysteroscopy, sigmoidoscopy, cystoscopy, cholecystectomy or dental procedures show a significant risk of progressing to peritonitis; hence the ISPD recommendation of preprocedural antibiotics in such cases. Even though 2005 ISPD guidelines recommended prophylaxis with minimal evidence, Yip et al. [21] in 2007 conducted a single-center study in which peritonitis occurred in 6.3% of 79 colonoscopies performed without antibiotic prophylaxis and none performed with antibiotic prophylaxis. Since then, most programs have been implementing preprocedural antibiotics. Gadallah’s study of 221 patients concludes that single-dose vancomycin is superior to single-dose cefazolin and reduces peritonitis prior to PD catheter insertion [22]. **Table 2** lists appropriate antibiotics before procedures, which are purely opinion-based.

<ul style="list-style-type: none">• Exit site care with topical mupirocin or gentamycin in all patients• Dental procedures<ul style="list-style-type: none">○ Amoxicillin 2.0 g 2 h before• Colonoscopy or GYN procedures:<ul style="list-style-type: none">○ Aminoglycoside overnight + oral metronidazole or ampicillin 1 g PO○ Fluconazole added in GYN procedures○ Perform procedures with dry abdomen and for a day afterwards• Antifungals when on systemic antibiotics to prevent secondary peritonitis

Adapted from ISPD [18].

Table 2. Preprocedural antibiotic prophylaxis to prevent peritonitis.

5. Presentation, diagnosis and management of peritonitis

Peritoneal dialysis patients have catheter embedded in their abdomen all the way to peritoneum. Infection can occur anywhere between the exit site of catheter, the tunneled area and the peritoneum. PD-related peritonitis is a local infection and only 20% of patients with peritonitis end up hospitalized. Catheters can get colonized with organisms, which sometimes form a biofilm. Mild trauma to the exit site may also cause peritonitis when conditions are favorable, as is the case with colonization and depressed immunity. Exit site infections could progress to tunneled infections and peritonitis if left untreated in most cases. Since most programs use antimicrobial prophylaxis, exit site infections are on the decline. ISPD 2017 recommends that the rate of catheter-related infections should be presented as numbers of episodes per year. Patients usually present with abdominal symptoms including abdominal pain, discomfort, vomiting or cloudy effluent. Fever with tachycardia and florid sepsis is seldom present. Patients should be asked about contamination during exchanges, signs of exit site infection, constipation, recent procedures, hospitalizations and recent antibiotic use for other systemic infections. A physical exam could reveal abdominal tenderness, redness at the exit site and should look for evidence of hernias.

Once peritonitis is suspected, empiric antibiotics should be started as soon as possible after drawing dialysate for cell count, culture and Gram stain. ISPD recommends collecting cultures of 5–10 mL of effluent in blood culture bottles. Peripheral blood cultures are taken only if the patient looks toxic and septic. Diagnosis requires that cell count be >100 cells/mm³ with appropriate symptoms. If $>50\%$ of WBCs are polymorph mononuclear leucocytes (PML), it is very likely that the patient has bacterial peritonitis even if the total cell count is <100 cells/mm³. It is recommended in APD to collect PD fluid after a dwell time of at least 2 h. One should be able to read a newspaper when effluent bag is laid over, which is a simple inexpensive test to see whether dialysate is cloudy, or not. Only cell count with appropriate cultures can confirm diagnosis though. Conditions that lead to cloudy effluent are listed in **Table 3** and criteria for diagnosis of peritonitis are listed in **Table 4**.

Most PD-related infectious peritonitis will have amylase levels of <50 IU/L in effluent and pancreatitis or other intra-abdominal pathology showing >50 IU/L, but one needs to note that icodextrin interferes with amylase assay and is not reliable. Systemic antibiotics are usually not needed since infection is local. Antibiotics via dialysate can be given intermittently every few days or continuously with every bag; programs may differ in their approaches. Nevertheless, if the patient is unresponsive to the intermittent approach for 3–4 days, a continuous approach is recommended. The decision to admit to inpatient service is generally dictated by the patient's general condition and degree of illness, rather than the underlying diagnosis of suspected PD-associated peritonitis. Most of these events will be treated in outpatient care.

Initial therapy with broad spectrum antibiotics is recommended as soon as possible for covering both Gram-positive and -negative organisms until culture results are available. For

Infectious peritonitis
Pancreatitis
Chemical peritonitis (medications, e.g., dihydropyridine calcium channel blockers [nifedipine, lercanidipine]))
Malignant ascites
Effluent eosinophilia
Sclerosing peritonitis
Chylous ascites
Specimen from dry abdomen

Table 3. Differential diagnosis of cloudy effluents.

1. Clinical, i.e. abdominal pain with our without cloudy dialysate
2. Effluent white cell count >100/μL or >0.1 × 10 ⁹ /L (dwell time of at least 2 h), and >50% polymorphs
3. Culture positive dialysate

Adapted from ISPD [20]. At least 2 of the above should be positive to diagnose peritonitis.

Table 4. Diagnosis of peritonitis.

Gram-positive organisms, vancomycin (with history of MRSA) or cephalosporins are recommended, as well as and ciprofloxacin, ceftazidime, cefepime or aminoglycosides tailored depending on whether the patient has significant residual renal function. Barretti conducted a proportionate meta-analysis and found that vancomycin and teicoplanin with ceftazidime were found to be superior to other regimens [23]. One needs to keep in mind sensitivities, common resistance patterns locally, the patient’s residual renal function and a history of peritonitis. The opacity of the fluid is expected to change from cloudy to clear in around 48–72 h. **Figure 1** lists the initial approach to peritonitis. In most cases, culture positivity can be established within 3 days. When the causative organism has been identified, subsequent cultures may be performed for monitoring, but when cultures remain negative after 3–5 days of incubation, cell count and differential, fungal, and mycobacterial cultures are to be repeated. Every organism’s interaction with the immune system is unique. Lin’s study of 52 patients provide evidence that local “immune fingerprints,” representative of specific organisms, are evident in said patients and differentiate between culture-negatives, Gram-positives or -negatives [24]. These immunologic biomarkers seem promising even though point of care tests have not yet been used widely.

Even though vancomycin is the preferred empiric therapy in methicillin-resistant *Staphylococcus aureus* (MRSA), there is no difference in cure rates for vancomycin and cefazolin when an appropriate cephalosporin dose is used in the context of methicillin-sensitive *Staphylococcus aureus*. It has been speculated that local (compartmental) antibiotic concentration with IP administration will greatly exceed concentrations serum concentrations, on which the general

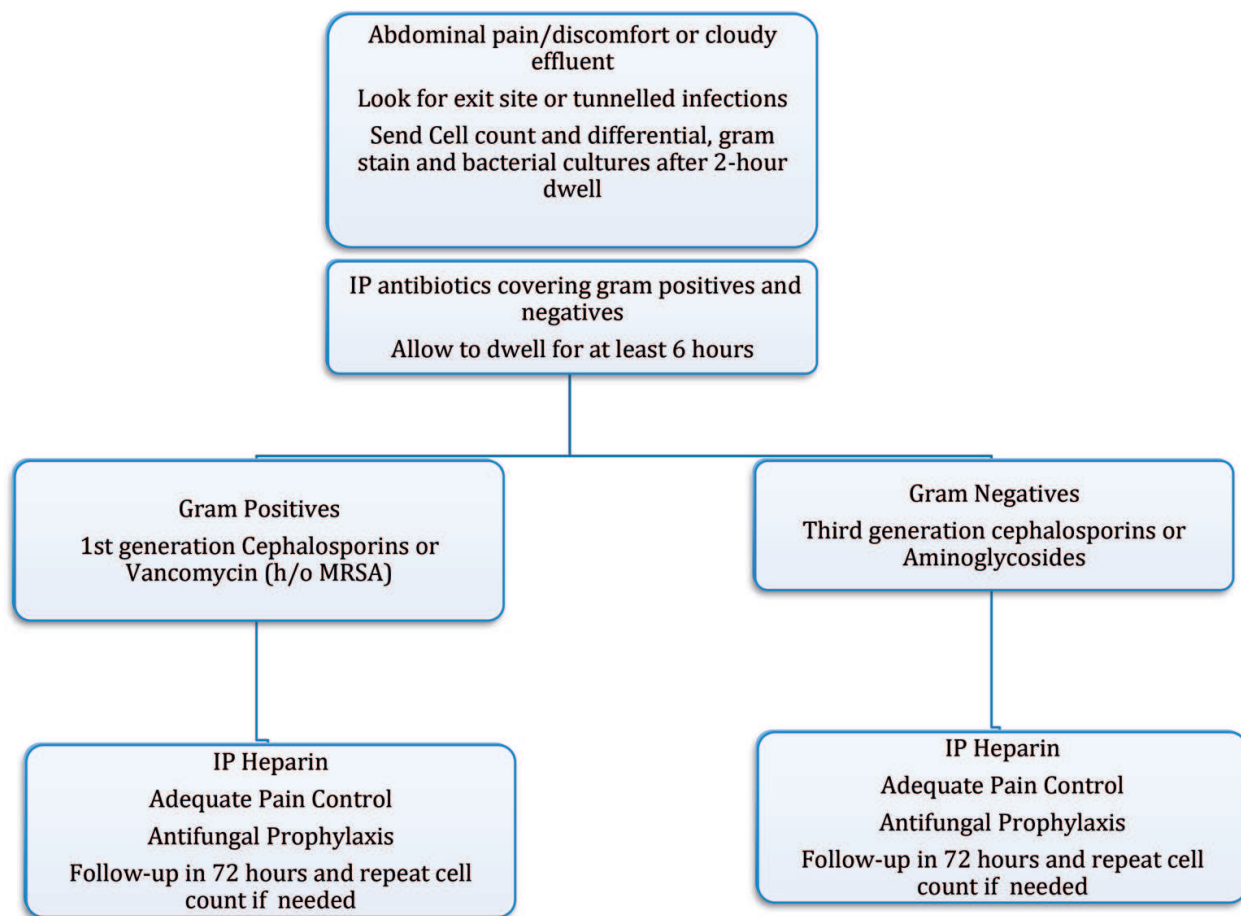


Figure 1. Initial approach to peritonitis.

concept of sensitivity is based upon. Ceftazidime, cefepime, aminoglycosides (e.g. gentamicin or netilmicin) or a carbapenem cover Gram-negatives adequately. Fluoroquinolones could be used if cultures show sensitivity, but there is an increased risk of Achilles tendon rupture in renal failure with fluoroquinolones. In patients allergic to cephalosporin, aztreonam could be used. Aminoglycosides demonstrate excellent Gram-negative activity and could be used in resource-poor nations where cost would be a barrier, as there is no evidence that short courses of aminoglycosides accelerate the loss of residual renal function [25] unless used for more than 3 weeks. Systemic absorption with a prolonged use of IP gentamycin can cause toxicity and might not correlate with systemic levels.

ISPD recommendations regarding the dosing of intraperitoneal (IP) antibiotics are listed in **Table 5**. These antibiotics should be administered using sterile techniques and IP use results in high local drug levels and is preferable to IV administration as peritonitis is mostly local and antibiotics are delivered at high concentration to the infected compartment, including to ensure the penetration of infected biofilms on peritoneal catheters [26]. Intermittent dosing should be dwelled for at least 6 h to allow for adequate absorption. IP vancomycin is dosed every 4–5 days, keeping serum trough levels above 15 µg/mL even though most programs do not check systemic levels. For patients on APD, intermittent doses of IP can be administered,

Aminoglycosides	Intermittent (1 exchange daily)	Continuous (all exchanges)
Amikacin	2 mg/kg daily	LD 25 mg/L, MD 12 mg/L
Gentamicin	0.6 mg/kg daily	LD 8 mg/L, MD 4 mg/L
Netilmicin	0.6 mg/kg daily	MD 10 mg/L
Tobramycin	0.6 mg/kg daily	LD 3 mg/kg, MD 0.3 mg/kg
<i>Cephalosporins</i>		
Cefazolin	15–20 mg/kg daily	LD 500 mg/L, MD 125 mg/L
Cefepime	1000 mg daily	LD 250–500 mg/L, MD 100–125 mg/L
Cefoperazone	No data	LD 500 mg/L, MD 62.5–125 mg/L
Cefotaxime	500–1000 mg	no data on daily dosage
Ceftazidime	1000–1500 mg daily	LD 500 mg/L, MD 125 mg/L
Ceftriaxone	1000 mg daily	No data
<i>Penicillins</i>		
Penicillin G	No data	LD 50,000 unit/L, MD 25,000 unit/L
Amoxicillin	No data	MD 150 mg/L
Ampicillin	No data	MD 125 mg/L
Ampicillin/sulbactam	2 g/1 g every 12 h	LD 750–100 mg/L, MD 100 mg/L
Piperacillin/tazobactam	No data	LD 4 g/0.5 g, MD 1 g/0.125 g
<i>Others</i>		
Aztreonam	2 g daily	LD 1000 mg/L, MD 250 mg/L
Ciprofloxacin	No data	MD 50 mg/L
Clindamycin	No data	MD 600 mg/bag
Daptomycin	No data	LD 100 mg/L, MD 20 mg/L
Imipenem/cilastatin	500 mg in alternate exchange	LD 250 mg/L, MD 50 mg/L
Ofloxacin	No data	LD 200 mg, MD 25 mg/L
Polymyxin B	No data	MD 300,000 unit (30 mg)/bag
Quinupristin/dalfopristin	25 mg/L in alternate exchange ^a	No data
Meropenem	1 g daily	No data
Teicoplanin	15 mg/kg every 5 days	LD 400 mg/bag, MD 20 mg/bag
Vancomycin	15–30 mg/kg every 5–7 days ^b	LD 30 mg/kg, MD 1.5 mg/kg/bag
<i>Antifungals</i>		
Fluconazole	IP 200 mg every 24–48 h	No data
Voriconazole	IP 2.5 mg/kg daily	No data

Courtesy of ISPD 2016 [20].

^aGiven in conjunction with 500 mg intravenous twice daily.

^bSupplemental doses may be needed for APD patients.

Table 5. Intraperitoneal antibiotic dosing recommendations for treatment of peritonitis.

Drug	Dosing
<i>Anti-bacterials</i>	
Ciprofloxacin	Oral 250 mg BD
Colistin	IV 300 mg loading, then 150–200 mg daily
Ertapenem	IV 500 mg daily
Levofloxacin	Oral 250 mg daily
Linezolid	IV or oral 600 mg BD
Moxifloxacin	Oral 400 mg daily
Rifampicin	450 mg daily for BW <50 kg; 600 mg daily for BW ≥50 kg
Trimethoprim/sulfamethoxazole	Oral 160 mg/800 mg BD
<i>Antifungals</i>	
Amphotericin	IV test dose 1 mg; starting dose 0.1 mg/kg/day over 6 h; target dose 0.75–1.0 mg/kg/day
Caspofungin	IV 70 mg loading, then 50 mg daily
Fluconazole	Oral 200 mg loading, then 50–100 mg daily
Flucytosine	oral 1 g/day
Posaconazole	IV 400 mg every 12 h
Voriconazole	Oral 200 mg every 12 h
Adapted from ISPD 2016 [20]. BD, twice a day; IV, intravenous; BW, body weight.	

Table 6. Systemic antibiotic dosing recommendations for the treatment of peritonitis.

Organism	Duration of treatment
Coagulate negative <i>Staphylococcus aureus</i>	2 Weeks
<i>Staphylococcus aureus</i>	3 weeks
Streptococcus	2 weeks
Enterococcus	3 weeks
Most Gram-negative bacilli	3–4 weeks
Stenotrophomonas species	3–4 weeks
Pseudomonas	3–4 weeks
Mixed Gram-positive and Gram-negative organisms	3 weeks
Multiple Gram-positive organisms	3 weeks
Fungal organisms (immediate catheter removal)	2–3 weeks post catheter removal
Corynebacterium species	3 weeks

Table 7. Duration of treatment of PD peritonitis by organism type.

Fungal peritonitis
Failed treatment for mycobacterial and polymicrobial infections
Refractory peritonitis
Relapsing peritonitis
Refractory exit site and tunneled infections

Table 8. Indications for catheter removal.

utilizing a day dwell of APD, or alternatively, a temporary change to CAPD might become necessary. Heparin at a dose of 500 units/L may be added to the PD fluid to decrease fibrin formation. In patients with biofilm in the catheter, the administration of oral rifampicin and IP urokinase to disrupt the catheter-associated biofilm resulted in catheter salvage in 64% of cases [27]. Chow analyzed outcomes of 565 consecutive episodes of peritonitis in relation to dialysate cell counts and concluded that effluent WBC count $\geq 1090/\text{mm}^3$ on day 3 was an independent prognostic marker for treatment failure [28]. The dosing of systemic antibiotics per ISPD recommendation is listed in **Table 6**. After empiric initial treatment, antibiotics are tailored depending on culture results with a duration of treatment determined by the type of organism affected (**Table 7**).

Mycobacterial infections are rare but present a challenge to diagnosis and should therefore be considered in the appropriate patients (living in third world or developed countries with endemic areas or history of travel) with persistent symptoms despite optimal periods of time on antibiotics. When effluent cultures are negative by day 3 (culture-negative peritonitis), cell count with differential should be repeated; if symptoms persist, effluent should be tested for tuberculous and nontuberculous mycobacteria in conjunction with a continuation of antibiotics for Gram-positive organisms. Aminoglycoside antibiotics should be discontinued if the patient remains asymptomatic with negative cultures. Native kidneys can clear antibiotics and there is higher risk of treatment failure in patients with significant residual renal function especially in Gram-positive and culture-negative patients [29]. Guidelines for the removal of catheters are listed in **Table 8**.

6. Standard definition with types of peritonitis (not based on type of organism)

6.1. Recurrent

Occurs within 4 weeks of completed therapy of previous episode with new organism. Carries worse prognosis than relapsing and repeat peritonitis. If polymicrobial or enteral organisms are seen, would need surgical evaluation and appropriate imaging of abdomen. Catheter removal should be considered.

6.2. Relapsing

Occurs within 4 weeks of completion of therapy of previous episode with the same organism. Lower rate of cure reported and catheter removal should be considered, especially if there is a suspected bacterial colonization of catheter. Sonography of catheter tunnel is also recommended.

6.3. Repeat

Occurs more than 4 weeks post-therapy of a prior episode with the same organism. Risk is highest 3 months after an episode and remains high for next 24 months [19]. Reevaluate antibiotic dosage and optimal duration of treatment. Further management depends on antibiotic sensitivity and might consider adding a second antibiotic for synergy although no evidence exists for this recommendation. Catheter removal could be considered depending on clinical status of patient.

6.4. Refractory

Effluent fails to clear after 5 days of appropriate therapy. Treatment includes immediate removal of PD catheter and intravenous antibiotics.

6.5. Catheter-related peritonitis

Exit site or tunnel infection progressing to peritonitis with the same organism. Sonogram of catheter tunnel if no signs of tunneled infection. Exit site infections that do not progress to peritonitis can be treated with oral antibiotics. If refractory exit site or tunneled infection is diagnosed, one should consider removal of the PD catheter.

6.6. Eosinophilic peritonitis

Cloudy effluent with >15% eosinophils. Could be seen in parasitic, tuberculous or fungal infections, or during recovery from bacterial peritonitis. Also seen with allergy to components of dialysate or catheter material and is usually self-limited needing no treatment, except with severe symptoms where treatments including steroids have been tried.

7. Summary

Peritoneal dialysis can cause infectious and noninfectious complications and peritonitis is one of the most common infectious complications. Peritonitis causes alteration of membrane transport characteristics leading to ultrafiltration failure and, with repeated episodes, will evolve into encapsulating peritoneal sclerosis. Multiple hospitalizations, transfer to hemodialysis and malnutrition-related complications could result in increasing health care costs in an era where pay for performance is advocated. There has been an increasing trend in

Gram-negative infections and decrease in Gram-positive infections [30, 31]. Intensive quality improvement projects, root cause analysis of adverse events, aggressive retraining and other prevention strategies discussed above should be implemented to decrease a potentially preventable adverse event and achieve improved outcomes.

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Author details

Sohail Abdul Salim^{1,2*} and Tibor Fülöp^{3,4}

*Address all correspondence to: sabdulsalim@umc.edu

1 Department of Internal Medicine, Division of Nephrology, University of Mississippi Medical Center, Jackson, Mississippi, USA

2 Central Nephrology Associates, Jackson, Mississippi, USA

3 Department of Internal Medicine, Division of Nephrology, Medical University of South Carolina, Charleston, South Carolina, USA

4 Ralph H. Johnson VA Medical Center, Charleston, South Carolina, USA

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