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Chapter 7

Infectious Complications in Peritoneal Dialysis: The Spectrum of Causative Organisms and Recommended Treatment Options

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/64005

Abstract

Peritoneal dialysis (PD) has become a real alternative to hemodialysis (HD) in recent decades, with comparable survival rates, lower costs, and improved patient quality of life. Nevertheless, PD-related infections, including peritonitis, exit-site infections (ESI), and tunnel infections, are important complications, resulting in significant morbidity and a 3.5–10.0% risk of death. Patients with peritonitis usually present with cloudy PD-fluid and abdominal pain; however, PD-associated peritonitis should always be included in differential diagnosis of PD patients with abdominal pain. The most common causative organisms for PD-associated peritonitis are gram-positive bacteria; however, gram-negative species are clinically important, due to the antibiotic resistance. The selection of empiric antibiotics depends on the center-specific distribution of microorganisms and antimicrobial susceptibility profiles. Typically, a first-generation cephalosporin is used in combination with broad gram-negative coverage (e.g., aminoglycoside, ceftazidime, or cefepime). High levels of methicillin-resistant *Staphylococcus epidermidis* or *Enterococcus* spp. strains require the use of vancomycin in many centers. Furthermore, for patients without clinical improvement after 5 days, or with fungal peritonitis, catheter removal is indicated.

Keywords: exit-site infections, tunnel infections, CAPD, peritonitis, infectious complications

1. Introduction

Georg Ganter published the first trial of peritoneal dialysis (PD) for treatment of uremia in the early twentieth century [1]. Over the following five decades, the technique was developed and mainly used as a procedure in acute kidney failure (AKI) [2], or rarely for patients with chronic kidney disease (CKD) [2]. In 1978, Popovich et al. described a novel sustainable PD technique, which became known as "continuous ambulatory peritoneal dialysis" (CAPD) [3]. CAPD facilitated the introduction of ambulatory PD and paved the way for the widespread use of this renal replacement therapy [4, 5]. When it was initially introduced, the combined 2-year survival rate of patients undergoing CAPD in Europe was only approximately 30% [6].

Over time PD has developed into a real alternative to hemodialysis (HD) with comparable survival rates, lower costs, and improved quality of life for patients [6–9]. Nevertheless, PD-related infections, including peritonitis, exit-site infections (ESI), and tunnel infections, are important complications, resulting in significant morbidity and a 3.5–10.0% risk of death [10]. Consequently, peritonitis is a leading cause of PD failure, resulting in transfer to HD [10, 11], with the associated reduced quality of life for patients [12] and increased costs to the health system [13]. The incidence of peritonitis decreased substantially with the development of disconnect (twin bag) systems and Y-systems [14, 15]. Nowadays, the incidence of PD-associated peritonitis varies from 0.06 to 1.66 episodes/patient-year depending on the center and country [16].

2. Clinical presentation and epidemiology

Patients with peritonitis usually present with cloudy PD-fluid and abdominal pain; however, PD-associated peritonitis should always be included in the differential diagnosis of PD patients with abdominal pain, even if the effluent is clear [17]. Furthermore, cloudy effluent can also be indicative of a different underlying disease [18, 19]. In principle, differential diagnoses of cloudy effluent could include, one the one hand, PD-associated infectious peritonitis (culture positive or culture negative), chemical peritonitis (culture negative), or eosinophilia of the effluent (culture negative); or, on the other hand, rare events like malignancy, chylous effluent, or an error of effluent sampling (e.g., a sample taken from a "dry" abdomen). With the introduction of Y-connectors peritonitis rates declined to around 0.7 episodes/patient year (one episode every 18 months; **Figure 1**) [17]; however, overall episode rates as low as one every 41–52 months (0.29–0.23/year) have been reported [15, 20, 21] and ISPD-guidelines recommend that every PD program should monitor infection rates annually at minimum [17]. Definitions and terminology describing PD-associated peritonitis episodes are provided in **Table 1**.

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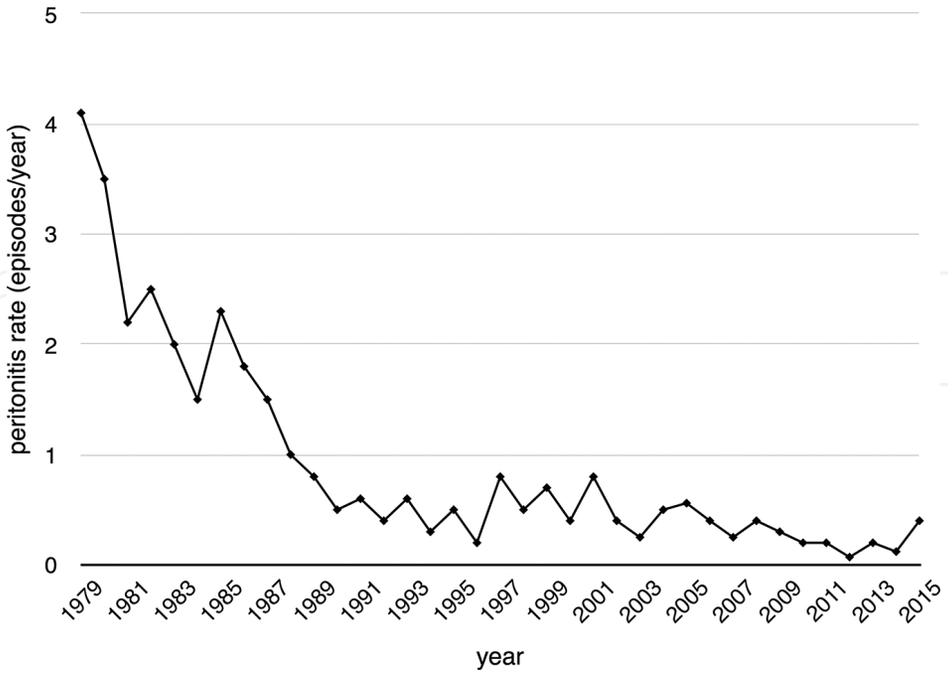

Figure 1. Decreasing peritonitis rates over recent decades. The International Society for Peritoneal Dialysis (ISPD) recommended a goal peritonitis rate of 0.7 per patient year.

Term	Definition
Peritonitis	At least two of the criteria*: abdominal pain, effluent with WBC >100/μL (after a dwell time of at least 2 h) and ≥50% polymorphonuclear neutrophilic cells, positive effluent cultures
Exit-site infection	Purulent drainage from the exit site. Erythema may or may not represent exit-site infection
Tunnel infection	Sonographic evidence of fluid collection (sonolucent zone around the catheter) with or without involvement of the proximal cuff (often clinically occult)
Catheter-related peritonitis	Peritonitis in combination with an exit-site or tunnel infection with the same organism, or one site sterile
Recurrent peritonitis	An episode that occurs within 4 weeks of completion of therapy for a prior episode but with a different organism
Relapsing peritonitis	An episode that occurs within 4 weeks of completion of therapy for a prior episode with the same organism or one sterile episode
Repeating peritonitis	An episode that occurs more than 4 weeks after completion of therapy for a prior episode with the same organism
Refractory peritonitis	Failure of the effluent to clear after 5-day treatment with appropriate antibiotics

Adapted with permission from Li et al. [17].

*Peritoneal dialysis patients presenting with cloudy effluent should be presumed to have peritonitis [1].

Table 1. Important terminology in PD-associated peritonitis

There are four main routes of entry for peritonitis-causing organisms. The most common path of infection is touch contamination at the time of exchange [22], which is the reason for the predomination of gram-positive strains of skin flora. In some patients with a history of antibiotic use, gram-negative strains can potentially be more numerous on the skin, which may elevate the risk of both gram-negative and fungal peritonitis [23, 24]. In addition, fecal contamination extends the spectrum of causative organisms toward gram-negative strains [25]. The second path of infection is catheter-related (exit-site and/or tunnel infection), and the third is the hematogenous route, although this is very rare [26]. The fourth route of infection in CAPD patients is endogen peritonitis (enteric or gynecological). Common reasons for this type of infection are endoscopic procedures (that require antibiotic prophylaxes [17], possibly abdominal surgery (some centers apply a temporary cessation of PD for 2 weeks for patients undergoing abdominal surgery [27]) and hollow organ or intestinal perforation. Perforation of abdominal organs should always be suspected in peritonitis patients with polymicrobial infections, no response to empiric antibiotic therapy, and a severe clinical course. Abdominal computed tomography (CT) scan should be performed rapidly, although such scans are frequently not diagnostic in this population; hence, early surgical referral is imperative [28, 29]. Peritonitis due to bowel leak (diverticulosis) without intestinal perforation can be managed without surgery; however, an antifungal prophylaxis should be applied [30].

3. Diagnostic work up

3.1. Cell count

Cloudy effluent should always trigger suspicion of peritonitis. Elevated white cell count (>100/μL), polymorphonuclear (PMN) cells >50%, and positive culture are diagnostic for peritonitis [17]. After catheter implantation, an elevated cell count with eosinophilia, in reaction to the introduction of artificial substances into the body, is common [31, 32] and fungal infections may also rarely be associated with eosinophilia [33, 34].

3.2. Culture

Microbiological culture is essential, not only for diagnosis, but also for the choice of anti-infection therapy [17]. Although blood cultures are rarely positive, they should be performed if an additional systemic inflammatory response syndrome is detected. Use of gram stain is controversial but is recommended in the current ISPD-guidelines [17] and can result in early diagnosis of infections [35].

3.3. Tunnel ultrasound

Tunnel ultrasound is an important tool to detect fluid collection, particularly in clinically occult tunnel infections [36–38]. This is important, since in patients with exit-site infections, additional tunnel infection increases the risk of catheter-associated peritonitis and loss of catheter [39].

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3.4. Abdominal imaging

Abdominal imaging is not recommended as standard but must be considered at an early stage when endogenous peritonitis is suspected [28–30].

4. Causative pathogens

4.1. Gram-positive organisms

The most important causative organisms for PD-associated peritonitis are gram-positive bacteria and, in most centers, coagulase negative staphylococci (CNS) are the most frequent cause of peritonitis [40] (**Figure 2**). Further, *Staphylococcus aureus* can also cause peritonitis, albeit in a smaller proportion of cases; however, infections with this organism should not be underestimated since *S. aureus* peritonitis is a serious complication of PD associated with increased mortality [41, 42]. The majority of recent studies have reported decreases of both CNS and *S. aureus* infections [43, 44] since the introduction of double-bag (twin-bag) and Y-connectors, nasal *S. aureus* screening, and local treatment with mupirocin [45–47]. Otherwise, methicillin-resistant *S. epidermidis* (MRSE) is the most common methicillin-resistant strain [44, 48], whereas methicillin-resistant *S. aureus* (MRSA) is rare [20, 44, 48].

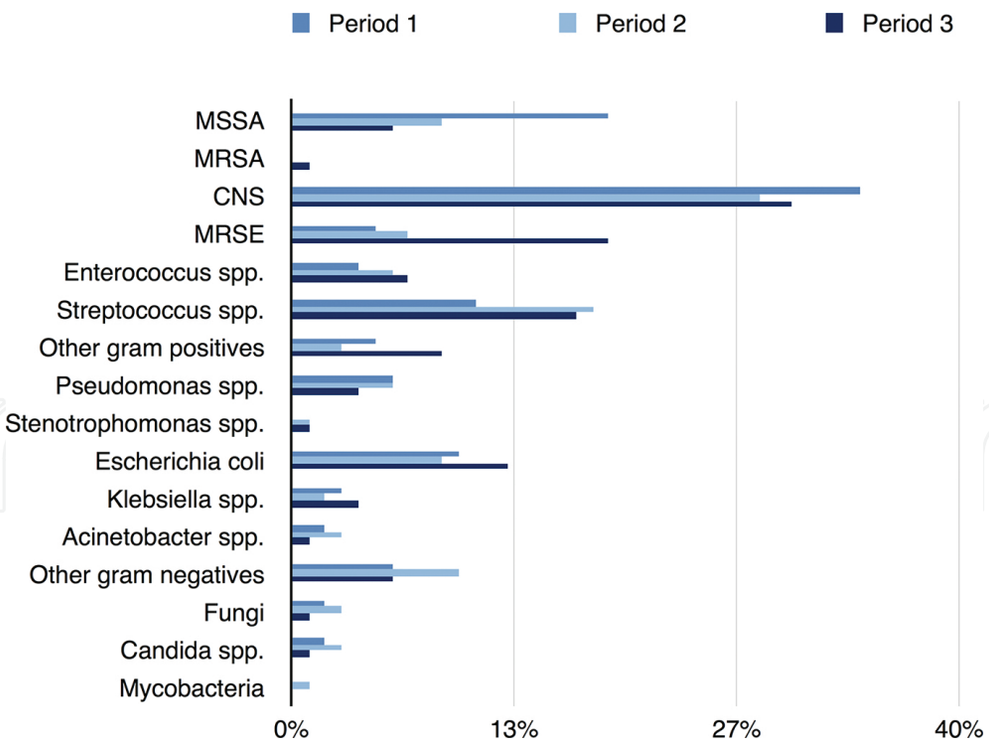

Figure 2. Causative pathogens in a single German center [44]. Distribution of organisms in period 1 (1979–1992), period 2 (1993–2003), and period 3 (2004–2014); all variables are expressed as percentages. Abbreviations: MSSA, methicillin-sensitive *S. aureus*; MRSA, methicillin-resistant *S. aureus*; CNS, coagulase-negative staphylococci; MRSE, methicillin-resistant *S. epidermidis*.

4.2. Gram-negative organisms

Whether or not gram-negative peritonitis is increasing which remains a topic of discussion and is likely to depend on various local factors [49–51]. The perception that gram-negative peritonitis is increasing may be a consequence of the recent pronounced decrease in gram-positive peritonitis, in the context of gram-negative peritonitis rates that remain constant or are less markedly decreased [44, 52, 53]. Gram-negative organisms are often resistant to antibiotics due to either plasmid encoded beta lactamase (e.g., extended beta lactamase (ESBL) producers) or chromosomally mediated beta-lactamases (e.g., derepressed AmpC beta-lactamase). These organisms are summarized by the acronym SPICE (*Serratia*, *Pseudomonas/Providencia*, indole-positive *Proteus/Acinetobacter/Morganella*, *Citrobacter*, *Enterobacter*, or *Hafnia*) [54, 55]. In addition, third generation cephalosporin-resistant gram-negative (3GCR-GN) rods or ESBL producers [44, 56] are an increasing problem, with ESBL-producing *Escherichia coli* peritonitis associated with worse patient outcomes [57].

4.3. Fungal

The majority of fungal peritonitis episodes are associated with prior antibiotic therapy [17]. Fungal prophylaxis during antibiotic therapy should be considered to prevent *Candida* peritonitis in centers with high rates of fungal peritonitis [17], which is a serious complication frequently leading to catheter loss (up to 90% of cases) and an increased risk of death, compared to other organisms [58–61]. Therefore, prompt catheter removal is indicated after identification of fungi by microscopy or culture [17].

4.4. Mycobacterium

Mycobacteria-associated peritonitis is rare [44] and, in many patients, only diagnosed after catheter removal from patients with refractory peritonitis.

5. Treatment

5.1. Initial empiric treatment

The selection of empiric antibiotics will depend on the center-specific distribution of micro-organisms and antimicrobial susceptibility profiles [17]. Typically, a first-generation cephalosporin, such as cefazolin or cephalothin, is used in combination with a drug with broad gram-negative coverage. No significant differences in outcome resulting from treatment with cephalosporins compared to glycopeptides have been reported to date [62]; however, the increasing prevalence of MRSE strains has led to the use of vancomycin in many centers [44]. Moreover, where there is a significant local presence of *Enterococcus* spp., treatment with vancomycin as a first line antibiotic regimen is recommended [63].

Gram-negative coverage can in principle be achieved using an aminoglycoside, ceftazidime, cefepime, or carbapenem [17]. Given the increasing problems due to 3GCR-GN and ESBL

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resistance, carbapenems are an important class of drugs. In addition, imipenem/cilastatin has similar efficacy in the treatment of PD-associated peritonitis to that of cefazolin plus ceftazidime or netilmicin [64]. However, randomized controlled trials for the use of carbapenems in PD peritonitis are lacking; therefore, routine measurement of blood concentrations should be performed to limit the risk of under- or overdosing [65]. Commonly used anti-infectious drugs for empiric treatment in accordance with the current ISPD-Guidelines are summarized in **Table 2** [17].

	Intermittent (per exchange, once daily) or continuous (mg/L, all exchanges) application of anti-infective drugs
Gram-positive coverage	
First Generation Cephalosporins[a]	15 mg/kg/BW i.p.
Vancomycin	Loading dose 30 mg/kg/BW, repeated application every 5–7 days adapted to drug levels i.p.
Ampicillin	25 mg/L in each exchange
Linezolid	Oral 200–300 mg every day or linezolid 600 mg i.v. twice daily
Rifampicin (additional in MRSA peritonitis)	Oral 450 mg every day for <50 kg; 600 mg every day for >50 kg additional to vancomycin
Gram-negative coverage	
Cefepime	1000 mg i.p.
Ceftazidime	1000–1500 mg i.p.
Gentamicin/Tobramicin	0.6 mg/kg/BW i.p.
Ciprofloxacin	Loading dose 50 mg/L, maintenance dose 25 mg/L
Antifungal coverage	
Fluconazole	200 mg i.p. every 24–48 h
Amphotericin	1.5 mg/L in every bag
Gram-positive and gram-negative coverage	
Imipenem/cilastin	1 g two times per day i.p.

All dosage information are adapted with permission from Refs. [17, 66]. Doses of drugs with renal clearance in patients with residual renal function (defined as >100 mL/day urine output) should be empirically increased by 25%.

BW = body weight; IP = intraperitoneal; MRSA = methicillin-resistant *S. aureus.*

[a]Cefazolin or cephalothin.

Table 2. Dosing of common anti-infection drugs for empiric, intermittent intraperitoneal first-line regimens in CAPD

5.2. Subsequent treatment

5.2.1. CNS and other gram-positive organisms

In patients for whom microbiological culture results confirm CNS or other gram-positive strains, the current guidelines recommend continuation of empiric gram-positive coverage and endorse adaption of treatment to reflect the local susceptibility profile, if appropriate. Antibiotics targeting gram-negative organisms should simultaneously be stopped [17].

Clinical improvement should be reviewed in a standardized manner, and dialysis effluent cell culture counts repeated on days 3–5. In cases of clinical improvement (symptom-free patient, clear effluent), the antibiotic regimen should be continued for 14 days. It is important to be vigilant for exit-site infections, occult tunnel-infections and intra-abdominal abscesses. Furthermore, potential catheter colonization should be assessed [17].

In general, therapy should continue for 14 days; however, for patients with catheter infection, therapy should be prolonged to 14–21 days and catheter removal considered [17]. An alternative approach is for treatment to be continued for 1 week after cultures become negative and cell counts less than 100 cells/L are reached [67].

In the absence of clinical improvement (persisting symptoms, cloudy effluent), patient samples should be re-cultured and biofilm involvement considered. If no clinical improvement is achieved after 5 days treatment with appropriate antibiotics, the catheter must be removed [17, 19].

5.2.2. Enterococcus/Streptococcus

In the case of cultures positive for *Enterococcus* spp. or *Streptococcus* spp., the empiric antibiotic regime should alternate with continuous application of ampicillin at 125 mg/L to each bag. Cephalosporins for gram-negative coverage must be stopped and the use of an aminoglycoside for *Enterococcus* treatment considered. Furthermore, it is important to note that ampicillin and aminoglycosides should not be mixed together in the same solution bag. In cases, resistant to ampicillin, vancomycin should be administered.

If vancomycin-resistant *Enterococcus* (VRE) emerges, a streptogramin antibiotic (quinupristin/dalfopristin), daptomycin, or linezolid must be administered, although the choice of therapy should always be guided by local susceptibility profiles. As already explained, the choice of further treatment approach depends on clinical improvement.

Therapy for *Streptococcus* spp.-associated peritonitis is the same as that for patients with *Enterococcus* spp.; however, the therapy durations differ, at 14 and 21 days for *Streptococcus* spp. and *Enterococcus* spp., respectively [17].

5.2.3. S. aureus

In proven *S. aureus* peritonitis, the empiric gram-positive antibiotic regimen should be continued in accordance with local susceptibility profiles. If there is evidence for vancomycin-

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resistant *S. aureus*, linezolid, daptomycin, or quinupristin/dalfopristin should be used [17]. Gram-negative coverage should be stopped, and the exit-site closely evaluated.

In the rare cases where a methicillin-resistant strain is detected, the antibiotic regime should be adjusted to a glycopeptide antibiotic (vancomycin or teicoplanin); in addition, rifampin (600 mg/day orally in a single or split dose) can be administered for 5–7 days.

As mentioned above, therapy should then be customized depending on clinical improvement. For *S. aureus*, therapy duration is 21 days. In *S. aureus* peritonitis linked to catheter infection, a refractory infection must be suspected and catheter removal should be considered. If the catheter is removed, a period of 3 weeks must be observed before reinitiation of PD [17].

5.3. Culture negative

If first culture is negative on days 1 and 2, empiric therapy should be continued and dialysis effluent cell count and cultures repeated on day 3. If the patient improves clinically, therapy should be continued for 14 days. In patients without clinical improvement, fungi-associated peritonitis should be considered and special culture techniques for unusual causes (e.g., viral, mycoplasma, mycobacteria, *Legionella*) applied [17]. If microbial detection is achieved, the specific anti-infection therapy should be adjusted to the particular microorganism.

If the culture remains negative and no clinical improvement is achieved, the catheter must be removed. In this case, anti-infection therapy should be continued for at least 14 days after catheter removal [17].

5.3.1. Pseudomonas spp.

If culture indicates *Pseudomonas* spp., it is important to differentiate between peritonitis with catheter infection and peritonitis without catheter infection.

In patients with underlying catheter infection and *Pseudomonas* peritonitis, the catheter must be removed and antibiotic therapy should be continued for at least 14 days. The timing of resumption of peritoneal dialysis may be modified depending on clinical course [17]. If no evidence for exit-site infection or tunnel infection is present, two different antibiotic substances (e.g., *Pseudomonas* spp. effective cephalosporin, aminoglycoside, quinolone, or piperacillin) should be applied. Clinical improvement, dialysis effluent cell counts, and cultures should be assessed on days 3–5.

If patients recover, therapy should continue for at least 21 days. In patients without signs of clinical improvement after 5 days, the catheter should be removed [17].

5.3.2. Single gram-negative organism

In patients with proven single gram-negative peritonitis, *Stenotrophomonas* must be distinguished from other gram-negative species (*E. coli*, *Proteus*, *Klebsiella*, etc.). *Stenotrophomonas*-associated peritonitis must be treated similarly to *Pseudomonas*-associated peritonitis, using two different antibiotics with different mechanisms of action, based on the local sensitivity

pattern (e.g., oral trimethoprim/sulfamethoxazole in combination with quinolones). Again, clinical improvement should be reviewed and dialysis effluent cell count cultures repeated on days 3–5. In cases of clinical improvement, therapy can be resumed after a duration of 21–28 days [17], otherwise the catheter must be removed.

In gram-negative non-*Stenotrophomonas*-associated peritonitis, empiric therapy should be adjusted to account for local susceptibility profiles. Cephalosporins, aminoglycosides, or carbapenems may be indicated. Gram-positive coverage should be stopped. In cases of clinical improvement, antibiotic therapy should be continued for 14–21 days. If no clinical improvement can be achieved, the catheter must be removed [17].

5.3.3. Polymicrobial peritonitis

In patients with polymicrobial peritonitis, multiple gram-negative organisms or mixed gram-negative/gram-positive organisms must be differentiated from multiple gram-positive organisms which indicate touch contamination or catheter infection.

Mixed gram-negative/gram-positive infections or multiple gram-negative-infections should always raise suspicion of endogenous peritonitis. Anti-infection therapy should be changed to metronidazole in combination with ampicillin, ceftazidime, or aminoglycosides. Further, an abdominal CT-scan is suggested and urgent surgical assessment is required. In patients with "surgical" peritonitis, the catheter must be removed and anti-infection therapy should be continued for 14 days [17].

In patients with polymicrobial gram-positive peritonitis, without diagnosis of catheter infection, anti-infection therapy adapted to local susceptibility profiles should be continued for at least 21 days. In patients with catheter infection, the catheter should be removed [17].

5.4. Other indications for catheter removal

Other indications for catheter removal are refractory infections or relapsing episodes. Further, in catheter-related infections with or without formation of biofilms, catheter removal should be considered and fungal infections always require catheter removal [68]. In *Pseudomonas aeruginosa*-associated peritonitis, prompt catheter removal and a double *P. aeruginosa* effective antibiotic regimen should be followed [69].

6. Prevention

6.1. "Single shot" antibiotic treatment at catheter implantation

A systematic Cochrane review investigated prophylactic antibiotic use at catheter insertion versus no antibiotic application at implantation in four trials, including 355 patients. The authors concluded that the use of perioperative intravenous antibiotic prophylaxis significantly decreased the risk of early peritonitis compared to no treatment [70]. Consistent with these findings, an ISPD-position statement recommended that prophylaxis with a first

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generation cephalosporin (e.g., cefazolin) or vancomycin, and prophylaxis at catheter placement, should be considered in each PD program, taking into consideration any emerging local resistance to vancomycin [16].

6.2. Peritoneal access and the role of catheter design

Two large meta-analyses, including 859 patients, confirmed that the risk for PD-associated infections did not differ significantly with various catheter designs [71, 72]. Therefore, the current ISP-Guidelines recommend no specific catheter design to prevent peritonitis [16]. Regarding peritoneal access, no significant differences in the rate of peritonitis or exit-site infections were observed when laparoscopy versus standard laparotomy, or subcutaneous catheter insertion was used [72–75]. However, a minimally invasive approach results in higher 1-year catheter survival and less frequent catheter migration, compared to laparotomy, according to a recent meta-analysis [72].

6.3. Eradication of *S. aureus*

A 1990 study by Luzar et al. demonstrating that nasal carriers of *S. aureus* have an increased risk of ESI and peritonitis [76] underlies the implementation of *S. aureus* screening in some PD programs. A large meta-analysis, including a total of 14 studies, 1233 enrolled patients and a similarly large control group, showed that mupirocin application was associated with a significantly lower risk of ESI and peritonitis [77]. However, no randomized control trials (RCTs) comparing the effectiveness of applying mupirocin to the catheter exit site against placebo have been conducted to date, although Bernardini et al. investigated the topical application of gentamicin versus mupirocin in 133 patients in an RCT [78]. The authors showed an advantage for gentamicin versus mupirocin for reducing catheter infection and peritonitis rates [78]; however, the long-term application of gentamicin may results in gentamicin-resistant organisms [79], which can potentially complicate peritonitis. Regardless, the ISP recommends topical application of antibiotic to the catheter exit-site in all patients [16].

6.4. Antimycotic prophylaxis in PD patients receiving antibiotics

Patients who receive prolonged or repeated antibiotics are at increased risk of developing fungal peritonitis [17]. Two RCTs compared antifungal prophylaxis in PD patients receiving antibiotic therapy [80, 81]. Lo et al. found an advantage of Nystatin as an antifungal prophylaxis during any antibiotic therapy; however, the trial was conducted in a population with a high incidence of fungal peritonitis. Restrepo et al. investigated 420 patients who received antibiotics for PD-associated complications and compared fluconazol as prophylaxis versus placebo. Both studies found that prophylaxis reduced the relative risk of fungal peritonitis. The ISPD working group recommends that each PD program should monitor their history of fungal peritonitis and decide if an antifungal with antibiotic protocol would be beneficial, particularly for patients taking prolonged or frequent courses of antibiotics [16, 17].

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