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Abstract

Exit site infection (ESI) is an important clinical problem in peritoneal dialysis (PD) patients and is a significant cause of peritonitis and catheter loss. While most ESIs are caused by skin commensals, rising incidence of atypical and resilient organisms such as mycobacteria, *Pseudomonas* and *Burkholderia* species has been observed. The diagnosis and management of these emerging pathogen remain difficult and poorly defined. This chapter highlights the evaluation and management of ESI in PD patients. The clinical features, microbiology, and ultrasonographic findings are discussed. The general and specific management of ESI due to different organisms will also be elaborated. ESI is usually a clinical diagnosis, but the use of bedside ultrasound can help assess for any collection around the cuff and tunnel tract involvement. Topical prophylaxis remains an effective way to prevent ESI. While the majority ESIs are related to skin flora and can be managed successfully by topical or systemic antimicrobials, clinicians should be alert to the emergence of resistant and atypical microorganisms. Surgical treatment should be reserved for ESI refractory to medical treatment or those with associated peritonitis.

**Keywords:** exit site infection, peritoneal dialysis, diagnosis, prophylaxis, management

1. Introduction

Peritoneal dialysis (PD) is an important modality of renal replacement therapy and is gaining popularity in both developed and developing countries [1]. While PD is associated with lower treatment costs and better patient autonomy when compared to hemodialysis, the practice of PD is also burdened with various infectious and noninfectious complications. PD catheter (also known as Tenckhoff catheter) is an essential device for the performance of PD exchanges. However, the implantation of a PD catheter is associated with infective complications such as...
exit site infection (ESI), tunnel tract infections, and peritonitis. Repeated or fulminant PD peritonitis heralds adverse clinical outcomes such as catheter loss, peritoneal failure and patient mortality [2–4]. Therefore, prevention of peritonitis plays a crucial role in the care of PD patients. In this context, ESI constitutes a significant risk factor for peritonitis, and thus prevention and appropriate management of ESI can substantially diminish the risk of PD-related peritonitis [2–5], and thus improve overall patient outcomes.

2. Pathogenesis and microbiology of exit site infection in peritoneal dialysis patients

In most PD patients, colonization with microorganisms occurs shortly after the implantation of PD catheter. Colonization does not equate clinical infection, but predisposes PD patients to ESI, especially after exit site traumatization. Bacterial colonization of exit site is frequently followed by formation of biofilm, which promote further bacterial growth and void the colonizing microorganisms from antimicrobial treatments. The organisms that colonize the exit site are often the same pathogens responsible for ESI [6]. Common pathogens to cause ESI in PD patients include *Staphylococcus aureus*, coagulase negative staphylococcus (CNS), *Pseudomonas aeruginosa*, and other Gram-negative bacilli [2]. With the widespread application of exit site prophylaxis, there is a shift in causative agents for ESI. For instance, some studies have suggested that the use of mupirocin or gentamicin ointment may predispose patients to fungal exit site infections [7, 8]. There is also emergence of exotic organisms such as atypical mycobacteria, *corynebacteria* as well as *Burkholderia* species to cause ESI [2, 9–11]. Furthermore, the development of antibiotics resistance remains an important concern in the management of ESI.

2.1. Staphylococcus aureus

*S. aureus* is a Gram-positive coccus and a common skin commensal. It is one of the commonest causative agents for ESI in PD patients, and accounts for over 50% of ESI cases [6]. In general, *S. aureus* can be categorized into methicillin-sensitive *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA). Methicillin-resistant *S. aureus* (MRSA) refer to strains of *S. aureus* that have developed resistance to β-lactam antibiotics including penicillinase-resistant penicillins (methicillin, cloxacillin, etc.) and cephalosporins. One national survey conducted among nephrology units in the United States has reported that over 40% of isolates of *S. aureus* belong to the MRSA strains [12]. Diabetes mellitus, increased age, immunocompromised state and protracted hospital stay are common and important risk factors for MRSA infections [13]. MRSA is a frequent cause of ESI, tunnel tract infection and peritonitis in PD patients, and is associated with appreciable morbidity and mortality in dialysis populations [14–16].

2.2. Coagulase-negative staphylococcus

Coagulase-negative staphylococci (CNS) are skin flora that can cause ESI. *Staphylococcus epidermidis* and *Staphylococcus saprophyticus* are common CNS, and the former accounts for roughly 20% of all ESI [6]. Other CNS that can cause ESI include *Staphylococcus lugdunensis* and...
Staphylococcus warneri [17]. While most CNS will respond to first-generation cephalosporins or penicillinase-resistant penicillin, there is growing prevalence for methicillin-resistant CNS (MRCNS).

2.3. Other Gram-positive organisms

Corynebacterium species (e.g., diphtheroids) are common skin commensals which exhibit intrinsic resistance to many commonly used antibiotics such as β-lactams, clindamycin, macrolides, quinolones and gentamicin [18]. Other Gram-positive bacteria that can be associated with ESI include streptococcal species (e.g., Streptococcus sanguinus) and enterococcal species [2, 17].

2.4. Pseudomonas aeruginosa

P. aeruginosa is a Gram-negative rod-shaped bacterium that commonly causes ESI in PD patients and is responsible for 8% of all ESI [6]. P. aeruginosa is a notorious for its ubiquity and intrinsic resistance to many commonly used antibiotics. Furthermore, P. aeruginosa is also well recognized for biofilm formation which contributes the persistence of infection. With these properties, P. aeruginosa often causes refractory ESI, requires prolonged antibiotics and is also associated with high risk of catheter loss [19, 20]. Moreover, around 20% of patients develop P. aeruginosa peritonitis several months after the resolution of ESI [19].

2.5. Other Gram-negative organisms and anaerobes

Gram-negative bacilli are also important causes of ESI, and Escherichia coli accounts for about 4% of all cases of ESI [6]. Other Gram-negative organisms that can cause ESI include Klebsiella pneumoniae, Enterobacter species and Proteus mirabilis [17]. The emergence of extended spectrum β-lactamase (ESBL)-producing Gram-negative bacilli is an escalating threat in the management of ESI. Other emerging pathogens to cause ESI include Burkholderia cepacia, which is a hardy nonfermenting Gram-negative organism [10, 11]. Its intrinsic resistance to multiple commercially available antibiotics and easy transmissibility renders it a growing problem in dialysis units. Although, B. cepacia is associated with low risk of tunnel tract infection or peritonitis, it is associated with a high rate of recurrence after successful antibiotics treatment [11]. Occasionally, anaerobes (e.g., micrococcus) can be also isolated from ESI in PD patients [17].

2.6. Mycobacterium

Rapidly growing atypical mycobacteria are more frequent causative agents for ESI than Mycobacterium tuberculosis. Atypical mycobacteria that commonly cause ESI include M. chelonae, M. fortuitum and M. abscessus [9, 21]. It is postulated that the use of gentamicin may predispose patients to atypical mycobacterial infections due to selection pressure on other microorganisms [9]. ESI due to atypical mycobacteria require prolonged systemic antimicrobial treatments and is associated with high rates of catheter loss [21]. Although dialysis patients are at risk of M. tuberculosis infection, ESI due to M. tuberculosis is not common and usually occur as part of a disseminated tuberculosis infection.
2.7. Fungi

Fungal ESI is a rare cause of ESI, and Candida species (being skin flora) are the commonest fungi isolated in this context. Some literatures have suggested that the use of mupirocin or gentamicin ointment prophylaxis might increase the risk of fungal ESI [7, 8].

3. Clinical features and evaluation of exit site infection in peritoneal dialysis patients

ESI is characterized by purulent discharge from the exit site, and with or without erythema or induration at the exit site [2, 22]. Although erythema around the PD catheter in the absence of purulent discharge may represent early signs of ESI, this can also be normal skin reaction to recently implanted PD catheter or exit site traumatization. The presence of crust around the exit site or positive cultures from exit site without signs of inflammation, however, does not indicate an ESI. The spectrum of severity of ESI can range from increased crust formation, to erythema around the exit site, to serous or purulent discharge, to abscess formation, and to tunnel tract involvement. In this context, different grading systems have been proposed to document the clinical severity of ESI [22, 23]. Assessment of the exit site involves gross inspection of the exit site, palpation of the tunnel tract and expression of discharge from the exit site. The discharge should be sent for microbiological examination (Gram smear, culture and sensitivity pattern), which can guide further treatment decisions. Ultrasonography has also been used to assess ESI, especially with regard to local collections and tunnel tract involvements [24]. In this context, sonolucent zone (>1 mm thick) surrounding the external cuff after a course of appropriate antimicrobial therapy and the involvement of the internal cuff portends adverse clinical outcomes [24].

4. Prevention of exit site infection in peritoneal dialysis patients

Proper care of the exit site constitutes an integral component in the prevention of ESI. In the early postoperative period (~first 2 weeks), the exit site should be kept dry until it is well healed [22]. The exit site should be covered with sterile dressing and the change of dressing should be performed by experienced nursing staff before the patient is properly trained. After completion of PD training, the patient should be able to clean the exit site with antiseptic agents (e.g., povidone iodine or chlorhexidine) on daily or alternate day basis, and the exit site be constantly covered with sterile dressings [22].

Hand hygiene is a key measure to decrease ESI in PD patients. Good hand hygiene practices should be undertaken by patients, helpers and healthcare providers during routine handling of the PD catheter and its exit site [25]. In this regard, 70% alcohol-based hand rub is the most effective hand-sanitizing agent to be used before and after the handing of PD catheter and its exit site [26]. Alternative hand-sanitizing agents include antimicrobial-containing (e.g., 4% chlorhexidine) soap [26].
S. aureus is a frequent pathogen to cause ESI, and associated with PD-related peritonitis and catheter loss [27]. The application of exit site prophylaxis can markedly diminish the PD-related S. aureus infection and thus should be undertaken in all PD patients [7, 28]. In this context, topical mupirocin has demonstrated its effectiveness as prophylaxis for S. aureus ESI [7, 28–32]. In one previous observational study involving more than 700 new PD patients, the use of topical mupirocin as exit site prophylaxis leads to a significant reduction in both ESI (0.168 vs. 0.156 episodes per patient-year) and peritonitis (0.443 vs. 0.339 episodes per patient-year) [32]. Subsequent meta-analyses corroborated these observations and highlighted that topical mupirocin was associated with 60–70% decrease in both S. aureus ESI and peritonitis [29, 33]. The administration of intranasal mupirocin has been investigated in a large multi-center trial, which showed that intranasal mupirocin in PD patients with confirmed nasal S. aureus carriage prevent ESI but not peritonitis [34]. However, data that compared intranasal versus exit-site route of mupirocin prophylaxis are lacking.

Although the exit site prophylaxis with mupirocin has curbed S. aureus infection in PD patients, P. aeruginosa remains an important culprit for ESI. Gentamicin is an aminoglycoside that demonstrates good activity against both S. aureus and P. aeruginosa. The application of daily gentamicin ointment versus daily mupirocin ointment as exit site prophylaxis has been investigated in a multi-center double-blind randomized clinical trial. The results demonstrated that gentamicin and mupirocin are similarly effective in preventing S. aureus ESI but the former conferred an advantage on preventing Pseudomonas ESI. Notwithstanding, liberal administration of gentamicin ointment as exit site prophylaxis might predispose PD patients to fungal ESI. Other novel prophylactic therapies for PD exit site include MediHoney and Polysporin triple (bacitracin, gramicidin and polymixin B) ointment [8, 35].

5. Management of exit site infection in peritoneal dialysis patients

5.1. General principles (Figure 1)

Exit site care and local dressing constitutes the cornerstone in the management of ESI. Topical antiseptics (e.g., mupirocin, gentamicin ointment) are all viable options for dressing of exit sites. Other alternatives such as hypertonic saline solution can be considered in selected cases (e.g., P. aeruginosa ESI). Empirical oral or intravenous antibiotics should be initiated after appropriate microbiological samples have been obtained and should always cover S. aureus. However, the choice of empirical antimicrobial treatment should also take into consideration the likely organism involved, medical background of the patients, previous culture and resistance profile of organisms isolated from the patient and the local antibiotics susceptibility/resistance pattern [2]. In general, first-generation cephalosporins or penicillinase-resistant penicillins can be used as initial treatment for ESI in PD patients [2]. The choice of antibiotics and duration of treatment can be further modified when the culture identity and the susceptibility/resistance profile are available. Trimming/shaving of the external cuff can be considered if the external cuff is partially or fully protruding outside the exit site [6, 36] (Figure 2). Catheters should be removed when there is recurrent infection due to the same organism, ESI
refractory to medical therapy, presence of tunnel tract abscess or associated peritonitis [2]. Most patients will require temporary hemodialysis while pending catheter reinsertion, simultaneous removal and reimplantation of PD catheter can be considered in selected cases to avoid bridging hemodialysis [37]. However, such approach is not advisable when there is also concomitant active peritonitis.

Figure 1. Management algorithm for exit site infection in peritoneal dialysis patients.

Figure 2. PD catheter after shaving of external catheter.

5.2. Management of exit site infection due to specific organisms

5.2.1. Methicillin-sensitive or resistant S. aureus

First-generation cephalosporins (e.g., cephazolin) or penicillinase-resistant penicillins (e.g., cloxacillin) can be used in MSSA ESI [2]. Parenteral vancomycin has established clinical efficacy
in the treatment of MRSA ESI, tunnel tract tunnel infection and peritonitis in PD patients [2]. In this context, intravenous (IV) vancomycin (1 g every 5–7 days for a minimum of 14 days) is a standard treatment of MRSA exit site or tunnel tract infection in PD patients [2]. However, rising MIC to vancomycin remains a valid concern for the use of vancomycin in MRSA infection. Other viable choices for MRSA infections in PD patients include teicoplanin, daptomycin, linezolid, tigecycline, and quinupristin-dalfopristin. Teicoplanin is a glycopeptide that exhibits activity and efficacy profile resembling vancomycin, and has the merit of longer half-life and superior tolerability than vancomycin. Daptomycin is an approved treatment of complicated MRSA soft-tissue infections and bacteremia (with or without infection endocarditis) in a dosage of 6 mg/kg/day [38, 39]. In CKD stage 4 or 5 patients, the dosage of daptomycin should remain unchanged but the frequency be reduced to every 48 hours [40]. Linezolid (600 mg B.I.D., IV or PO) can be used for the treatment of MRSA skin infection as well as community- or hospital-acquired MRSA pneumonia [41, 42]. No dosage modification is required for linezolid in dialysis patients but one should be aware of the side effects such as myelosuppression and lactic acidosis [42]. Tigecycline demonstrates promising \textit{in vitro} activity against most MRSA strains and is an approved treatment for MRSA skin and intra-abdominal infections [43–45]. No dosage reduction is required for the use of tigecycline in PD patients is another added advantage. Quinupristin-dalfopristin is an approved treatment for MRSA soft-tissue infections with no dosage modification in renal failure patients. However, its data in PD patients are relatively scarce [40]. Clindamycin is not recommended for MRSA ESI in PD patients due to its unreliable activity against MRSA acquired nosocomially [42, 46]. Other emerging antimicrobials for MRSA infections include lipoglycopeptides dalbavancin, telavancin and oritavancin as well as newer generation cephalosporins such as ceftobiprole and ceftaroline [43, 44, 47]. The data on these novel agents for MRSA ESI, however, remain limited in PD patients.

5.2.2. \textit{Pseudomonas aeruginosa}

Topical treatments (e.g., gentamicin ointment) can be used as adjunctive treatment for mild P. aeruginosa ESI [2]. Other alternatives include hypertonic saline although such therapy is not a standard practice [22]. Previous studies have reported the efficacy of oral fluoroquinolones (e.g., ciprofloxacin or levofloxacin) for the treatment of ESI due to P. aeruginosa [2, 19, 48]. Current standard-of-care therapy for the ESI consisted of oral fluoroquinolones (e.g., ciprofloxacin 500 mg B.I.D) and local application of antiseptic agents to the exit site [2, 19, 48]. Intravenous antibiotics should be used in severe ESI due to P. aeruginosa [2]. Choices of intravenous antibiotics include third- or fourth-generation cephalosporins (e.g., ceftazidime and cefepime), ticarcillin/clavulanate, piperacillin (with or without tazobactam) and carbapenems. The optimal duration of antibiotics treatment should be at least 2–3 weeks [2]. Catheter removal should be considered in cases with refractory ESI which respond poorly to medical treatment or associated peritonitis [2]. Up to 50–80\% of patients with ESI due to P. aeruginosa ESI respond to medical therapy, while approximately 20–36\% would require catheter removal [19, 48].
5.2.3. Other Gram-negative organisms

In general, ESI due to Gram-negative organisms are susceptible to second- or third-generation cephalosporins [2, 22]. However, there is increasing prevalence of ESBL-producing Gram-negative organisms. Carbapenems should be considered in patients with previous history of ESBL-producing organisms or when the ESI do not respond to second- or third-generation cephalosporins [2]. *B. cepacia* are generally susceptible to ceftazidime (95.5%), piperacillin/tazobactam (95.5%) and piperacillin (90.9%) [11]. While most patients with *B. cepacia* ESI will respond to medical therapy, a high rate of recurrence is observed. Similar to *P. aeruginosa* ESI, the duration of treatment for *B. cepacia* ESI should be extended up to 3 weeks.

5.2.4. Mycobacterium

The treatment regimen for atypical mycobacterium ESI is dependent on the organisms identified as well as the susceptibility/resistance profiles. In general, the regimen should consist of at least two or more antimycobacterial agents (e.g., parenteral aminoglycosides, fluoroquinolones, tetracyclines and macrolides), and prolonged therapy is generally required [2, 21]. In this context, a combination of oral fluoroquinolones, tetracyclines (doxycycline or minocycline), macrolides (clarithromycin or azithromycin) or cotrimoxazole can be administered for *M. fortuitum* ESI [21, 49]. Clarithromycin, in combination with doxycycline or ciprofloxacin, is commonly used in localities where most *M. chelonae* are susceptible to macrolides [21]. The treatment regimen for *M. abscessus* should comprise clarithromycin plus either amikacin or high-dose cefoxitin [21]. The prolonged administration of aminoglycosides and macrolides is associated with ototoxicity and cardiac arrhythmia (QT prolongation) in PD patients. Approximately 44% of patients will respond to medical therapy and catheter removal should be considered in patients with refractory mycobacterial ESI.

5.2.5. Fungal exit site infection

Fungal ESI is rare clinical entity and there are limited data regarding the optimal management of fungal ESI. It is important to exclude contamination when fungus is isolated from the exit site, and removal of PD catheter should be considered if there is established fungal ESI to avoid fungal peritonitis.

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