Peritoneal Dialysis International, Vol. 37, pp. 141–154
www.PDIConnect.com

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ISPD GUIDELINES/RECOMMENDATIONS

ISPD CATHETER-RELATED INFECTION RECOMMENDATIONS: 2017 UPDATE

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KEY WORDS: Infection; antibiotic; peritonitis.

INTRODUCTION

Peritoneal dialysis (PD) catheter-related infections are a major predisposing factor to PD-related peritonitis (1–3). The primary objective of preventing and treating catheter-related infections is to prevent peritonitis.

Recommendations on the prevention and treatment of catheter-related infections were published previously together with recommendations on PD peritonitis under the auspices of the International Society for Peritoneal Dialysis (ISPD) in 1983 and revised in 1989, 1993, 1996, 2000, 2005, and 2010 (4–9). The present recommendations, however, focus on catheter-related infections, while peritonitis will be covered in a separate guideline.

These recommendations are evidence-based where such evidence exists. The bibliography is not intended to be comprehensive. When there are many similar reports on the same area, the committee prefers to refer to the more recent publications. In general, these recommendations follow the Grades of Recommendation Assessment, Development and Evaluation (GRADE) system for classification of the level of evidence and grade of recommendations in clinical guideline reports (10). Within each recommendation, the strength of recommendation is indicated as Level 1 (We recommend), Level 2 (We suggest), or Not Graded, and the quality of the supporting evidence is shown as A (high quality), B (moderate quality), C (low quality), or D (very low quality). The recommendations are not meant to be implemented in every situation indiscriminately. Each PD unit should examine its own pattern of infection, causative organisms, and sensitivities and adapt the protocols according to local conditions as necessary. Although many of the general principles presented here could be applied to pediatric patients, we focus on catheter-related infections in adult patients. Clinicians who take care of pediatric PD patients should refer to the latest consensus guideline in this area for detailed treatment regimen and dosage (11).

DEFINITIONS

- We suggest that exit-site infection is defined as the presence of purulent discharge, with or without erythema of the skin at the catheter-epidermal interface (not graded).
- We suggest that tunnel infection is defined as the presence of clinical inflammation or ultrasonographic evidence of collection along the catheter tunnel (not graded).

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Received 14 September 2016; accepted 15 September 2016.

Perit Dial Int **2017; 37(2):141–154**
https://doi.org/10.3747/pdi.2016.00120

In this guideline, catheter-related infections are used as the collective term to describe both exit-site infection (ESI) and tunnel infection. These 2 conditions may occur on their own or simultaneously. Exit-site infection is diagnosed by the presence of purulent drainage, with or without erythema of the skin at the catheter-epidermal interface (12,13). Pericatheter erythema without purulent drainage is sometimes an early indication of infection but can also be an allergic skin reaction, or occur in a recently placed catheter or after trauma to the catheter (14). Clinical judgment is required to decide whether to initiate therapy or to follow carefully. A positive culture with a normal-appearing exit site is indicative of colonization rather than infection. A tunnel infection may present as erythema, edema, induration, or tenderness over the subcutaneous pathway but is often clinically occult, as shown by sonographic studies (15). A tunnel infection usually occurs in the presence of an ESI but could occur alone. Exit-site infections caused by *Staphylococcus aureus* or *Pseudomonas aeruginosa* are often associated with concomitant tunnel infections (16).

INFECTION RATE

- We recommend that every program should monitor, at least on a yearly basis, the incidence of catheter-related infections **(1C)**.
- We suggest that the rate of catheter-related infection should be presented as number of episodes per year **(not graded)**.

As part of a continuous quality improvement (CQI) program, all PD programs should monitor the incidence of catheter-related infections on a regular basis (17,18). There are several methods of reporting the rate of catheter-related infections (8,19). The committee favors reporting the rate of catheter-related infections as number of episodes per year because data are presented in a linear scale and easy to compare. In addition to the overall rate of catheter-related infections, monitoring may also include the rates of ESI and tunnel infection separately, as well as the infection rate of specific organisms (especially *Staphylococcus aureus* and *Pseudomonas* species) and the spectrum of antibiotic sensitivity (20). With this information, interventions can be implemented when infection rates are rising or unacceptably high. However, there are insufficient data at present to suggest a minimum target for the rate of ESI and tunnel infection.

PREVENTION OF CATHETER-RELATED INFECTIONS

Many prevention strategies aim primarily to reduce the incidence of peritonitis, and clinical trials in this area often report the rate of ESI or catheter-related infections as a secondary outcome. In this guideline, we focus on the prevention of catheter-related infections. The prevention of peritonitis is described in a separate guideline.

CATHETER PLACEMENT

- We recommend that prophylactic antibiotics be administered immediately before catheter insertion **(1A)**.
- No technique of catheter placement has been demonstrated to be superior to another for the prevention of catheter-related infections **(not graded)**.

Detailed description on the recommended practice of PD catheter insertion has been covered in another ISPD position paper (21). A systematic review of available prospective trials found that prophylactic perioperative intravenous (IV) antibiotics had no significant effect on the rate of early catheter-related infections, although the risk of early peritonitis was significantly reduced (22). There are 3 randomized controlled trials on the use of perioperative IV cefuroxime (23), cefazolin (24), and gentamicin (24,25) as compared with no treatment and reported early catheter-related infections (within 1 month after catheter placement) as a secondary outcome. One of them had no catheter-related infection in both study arms (23), 1 study that used cefazolin and gentamicin found no benefit (24), while the other that used gentamicin alone showed benefit (25). One additional study found that perioperative vancomycin, and to a lesser extend cefazolin, reduces the rate of early peritonitis, but the rate of catheter-related infection was not reported (26). No data exist on the effectiveness of routine screening and eradication of *S. aureus* nasal carriage before catheter insertion (e.g. by intranasal mupirocin).

Besides prophylactic antibiotics, various techniques of catheter placement have been tested. With the appropriate training, there is no difference in the rate of early ESI between catheters placed by nephrologists and surgeons (27,28). When percutaneous or laparoscopic techniques are compared with open catheter placement, one observational study reported a lower incidence of wound and ESI with the laparoscopic technique (29), while 3 other studies found no difference in the rate of early catheter-related infections between different techniques (30–32). Similarly, vertical tunnel-based low-site PD catheter implantation does not reduce the risk of ESI (33). Several randomized trials have compared laparoscopic or peritoneoscopic catheter placement with standard laparotomy, but none of them reported catheter-related infection as a secondary outcome (34). Two studies compared midline with lateral incision (35,36), but neither found any difference in the risk of catheter-related infection.

Before catheter insertion, it is advisable to carefully choose the location of the exit site so that it could be conveniently cleaned and the chance of inadvertent trauma (e.g. by the belt) is minimized (37). After catheter placement, it is generally considered good surgical practice to cover all incisions and leave the dressing undisturbed for 3 to 5 days so as to allow epithelialization and wound healing by primary intention (38). Although an uncontrolled study suggests that the technique of burying the PD catheter in subcutaneous tissue for 4 to 6 weeks after implantation is associated with a lower rate of catheter-related infections (39), 2 randomized controlled

studies found no difference as compared with the standard technique (40,41). It remains controversial whether immediate commencement of PD after catheter insertion is associated with a higher risk of catheter-related infections (42–45). The optimal time to start PD remains to be defined (46).

CATHETER DESIGN

- No particular catheter design has been demonstrated to be superior to another for the prevention of catheter-related infections **(not graded)**.

There are no convincing data regarding effect of PD catheter design and configuration on peritonitis risk. Eight randomized trials have compared straight and coiled PD catheters (36,47–53) and found no difference in the rate of catheter-related infections. Two systematic reviews, each with different exclusion criteria and neither of which included all 8 trials, reached the same conclusion (34,54). Two randomized controlled trials compared a swan neck design and the traditional Tenckhoff catheter and reported the rate of catheter-related infection as a secondary outcome (55,56). One found that the swan neck design had marginally lower risks of ESI and tunnel infection (55), while the other found a higher rate of ESI in the swan neck group but the result was not statistically significant (56). However, an extended swan neck catheter may be beneficial. One retrospective study on pre-sternal swan neck catheters (57) and another prospective study on extended swan neck catheters with upper abdominal exit site (58) found lower rates of catheter-related infections as compared with conventional abdominal catheters. An observational study reported that the use of a double-cuff catheter is associated with a reduction in *S. aureus* peritonitis, but the rate of ESI was not reported (59). A randomized controlled trial compared double-cuffed catheter with single-cuffed ones and found no difference in the rate of catheter-related infections (60). Another randomized controlled trial that compared downward direction of the exit site by swan neck catheter to lateral direction by conventional catheter reported a similar incidence of catheter-related infections between the groups (61).

An alternative peritoneal catheter exit-site location is sometimes needed in patients with morbid obesity, intestinal stomas, or urinary or fecal incontinence. In a prospective non-randomized study, 2-piece extended catheters, which permit pre-sternal exit site away from problematic abdominal conditions, was compared to conventional catheters (62). The result showed that although extended catheters enabled peritoneal access for patients in whom conventional catheter placement would be difficult or impossible, they were associated with a higher risk of relapsing peritonitis episodes, especially those caused by coagulase-negative staphylococcal species (62).

In addition to the conventional silicone catheter, early studies suggested that silver-ion coated or implanted catheters could minimize bacterial colonization and reduce the rate of catheter-related infections (63,64). However, this type of catheter is not widely available and the experience is limited. Antimicrobial-impregnated catheters have also been found to reduce PD catheter-related infections in rats (65), but further clinical trials are needed in this area.

CONNECTION METHODS

Several prospective studies compared the Y-connection systems with the "flush before fill" design with the traditional spike systems and reported the rate of catheter-related infection as a secondary outcome (66–70). Although they generally showed that the risk of peritonitis was reduced by the Y-systems, the rate of catheter-related infection was not reduced in any of these trials (66–70). Similarly, 3 randomized controlled trials compared the double-bag system with the Y-connection systems (both with the "flush before fill" design), and all found no significant difference in the rate of catheter-related infections (71–73).

TRAINING PROGRAMS

- We recommend that the latest ISPD recommendations for teaching PD patients and their caregivers be followed (74) **(1C)**.
- We recommend that PD training be conducted by nursing staff with the appropriate qualifications and experience **(1C)**.

The detailed recommended practice of PD training is covered in previous ISPD guidelines (74,75). Every PD program should prepare the trainers according to this document and develop a specific curriculum for training. Unfortunately, high-level evidence guiding how, where, when, and by whom PD training should be performed is lacking (76). Ideally, each patient should be trained by a dedicated nurse, whose time is totally focused on training the patient. However there are few published data on the optimal nurse-to-patient ratios or training protocols (76). It is difficult to define "appropriate qualification and experience," and there is conflicting evidence regarding the relation between nursing experience and clinical outcome (77,78).

The method of training is often believed to affect the risk of catheter-related infections (79,80). An observational study found that the rate of ESI was reduced 10-fold with a program that incorporated intensive training of nursing staff and patients, improved operative aseptic technique and reduction in *S. aureus* nasal carriage (81). The training program should include general theories of adult education as well as specific knowledge related to PD (74,75). One prospective non-randomized study showed that training programs that used an adult learning theory-based curriculum were associated with a lower rate of ESI as compared with non-standardized conventional training programs (82). One study reported that patients with better knowledge had better adherence to the recommended exchange protocols and lower rate of ESI (83). Two prospective studies showed that the duration of PD training and number of training lessons were associated

with the frequency of peritonitis (84,85), but the incidence of catheter-related infections was not reported in either of them. Two more studies reported conflicting results regarding the relation between nursing experience and peritonitis rate (77,78), but the incidence of exit-site or tunnel infection was not reported in either.

Adherence to the guideline recommendations and antiseptic procedures are important for maintaining a low incidence of catheter-related infections (86). After PD training is completed, a home visit by the PD nurse is usually recommended to detect problems with exchange technique, adherence to protocols, and other environmental and behavior issues that increase the risk of infections (87,88). One case controlled study reported that home visit programs are associated with improved technique survival of PD patients (89). However, the effect of a home visit on catheter-related infections has not been tested in a prospective study.

In addition to the initial training, regular retraining may help to reduce mistakes in performing practical procedures (90,91). Two observational studies suggested that re-training may reduce peritonitis related to touch-contamination, but the rate of catheter-related infections was not reported (90,92). The indication, optimal time, and content of retraining have not been well defined (76).

TOPICAL ANTIBACTERIAL AND ANTISEPTIC AGENTS

- We recommend daily topical application of antibiotic cream or ointment to the catheter exit site **(1A)**.
- We suggest that no cleansing agent has been shown to be superior with respect to preventing catheter-related infections **(2B)**.

A number of topical cleansing agents have been tested for the prevention of catheter-related infections (Table 1). Antibacterial soap and water are commonly used to clean the exit site, but that efficacy has not been formally tested. Povidone-iodine, chlorhexidine, and electrolytic chloroxidizing solutions have been used as disinfectants for routine care of the exit site to prevent catheter-related infections. Four randomized controlled trials compared topical povidone-iodine to simple soap and water cleansing for exit-site care or no treatment (93–96); 2 found that topical povidone-iodine reduced the incidence of ESI (93,94), the third showed no significant difference (95), while the last one showed that with topical mupirocin cream, topical povidone-iodine dressing confers no added benefit (96). The peritonitis rate was similar between povidone-iodine and control groups in all these studies.

TABLE 1
Topical Antibacterials, Antiseptics, and Cleansing Agents for the Prevention of Catheter-Related Infections

- povidone-iodine (93–95)
- chlorhexidine solution (97,103)
- Amuchina solution/hypochlorite solution (98–102)
- mupirocin cream (25,56,106–113)
- gentamicin cream or ointment (107,108,123)
- ciprofloxacin otologic solution (121)
- antibacterial honey (128)
- polysporin triple ointment (129)
- polyhexanide (131)

Chlorhexidine gluconate, 0.05% to 2% aqueous solution with or without isopropyl alcohol, is also commonly used. A randomized controlled trial showed that daily chlorhexidine care at the exit site is superior to normal saline cleansing for the prevention of exit site colonization by *S. aureus* (97). Four prospective studies showed that Amuchina solution (an electrolytic chloroxidizing solution containing sodium hypochlorite) at 3% to 10% is effective in preventing infection at the exit site, without any secondary topical reaction (98–101). The addition of sodium hypochlorite solution to topical mupirocin may further reduce the rate of ESI and peritonitis in pediatric PD patients (102). However, studies with head-to-head comparison of hypochlorite, chlorhexidine, or povidone-iodine reported conflicting advantage of one agent over another (103–105).

Daily application of mupirocin cream or ointment to the skin around the exit site could prevent ESI caused by *S. aureus*. This strategy is proved to be effective by a number of observational studies, randomized controlled trials, and meta-analyses (22,34,106–112) and has also been shown to be cost-effective (113). Although some meta-analyses also include studies on nasal mupirocin ointment, topical mupirocin over the exit site reduced the risk of *S. aureus* ESI by 72% in a pooled analysis (109). The optimal frequency of topical mupirocin, however, is not clearly defined. One retrospective study showed that once weekly application was less effective than thrice weekly administration (114). Mupirocin resistance has been reported, particularly with intermittent but not daily administration (115–118). The long-term implication of mupirocin resistance, however, remains unclear and may have been overstated (119). Although all catheters currently in use are made of silicone, it is important to note that some mupirocin ointment contains polyethylene glycol and has a deleterious effect on polyurethane devices (120). In PD patients with polyurethane catheters, a randomized controlled trial showed that topical application of ciprofloxacin otologic solution to the exit site reduced the rates of ESI caused by *S. aureus* as well as *Pseudomonas* species, as compared with soap and water cleansing only (121).

Other alternative topical antibacterial agents have been tested, often with an aim to reduce the risk of catheter-related infections caused by gram-negative bacteria (especially *Pseudomonas* species), which have become a common cause of catheter-related infections in recent years (122). A randomized controlled trial showed that daily application of gentamicin cream to the exit site was highly effective in reducing ESI caused by *Pseudomonas* species, and was as effective as topical mupirocin in reducing *S. aureus* ESI (107). Two subsequent prospective studies, however, found

no significant difference in the rates of ESI between topical gentamicin and mupirocin ointment and actually a marginally higher rate of gram-positive infections in the gentamicin group (108,123). Two observational studies further suggested that the change of prophylactic protocol from topical mupirocin to gentamicin was associated with an increase in ESI caused by *Enterobacteriaceae*, *Pseudomonas* species, and probably non-tuberculous mycobacteria (124,125). Topical gentamicin should be considered as an alternative to mupirocin for prophylactic application at the exit site. Alternating mupirocin/gentamicin is associated with increased risk of fungal peritonitis compared with gentamicin alone (126). The incidence and implications of gentamicin resistance are uncertain (127).

Other prophylactic strategies have been tested. The HONEYPOT study found that with standard exit-site care, the rate of catheter-related infection is similar between patients randomized to receive daily topical application of antibacterial honey to the catheter exit site and those treated with intranasal mupirocin ointment (128). In the subgroup analyses, honey actually increased the risk of ESI, tunnel infection, or peritonitis in diabetic patients (128). However, there was no direct comparison between application of topical antibacterial honey and mupirocin to the exit site. In the MP3 study, patients randomized to topical polysporin triple ointment had an insignificant trend of higher ESI rate than those treated with topical mupirocin to the exit site (129). A small randomized trial reported that topical application of 3% hypertonic saline is as effective as topical mupirocin cream for the prevention of ESI (130). Another study reported that topical polyhexanide resulted in a lower incidence of ESI than povidone-iodine (131). In contrast, topical polyhexamethylene biguanide was inferior to mupirocin in another randomized controlled trial, which was terminated after interim analysis (132). The effectiveness of nanotechnology antimicrobial spray dressing in preventing ESI has been reported in a pilot study (133). All these results should be regarded as preliminary, and further validation is needed.

OTHER ASPECTS OF EXIT-SITE CARE

- We recommend that the exit site be cleansed at least twice weekly and every time after a shower **(1C)**.

General measures on exit-site care and meticulous hand hygiene are generally recommended, but none has been proved by randomized controlled trial to reduce the rate of catheter-related infections (134). In general, the exit site should be cleansed at least twice weekly and every time after a shower (96,135). Immobilization of the catheter is often recommended, but there is no clinical trial to support this practice. Although gauze is commonly used for exit-site dressing and protection, a recent study suggested that regular dressing may not be necessary (96). Agents other than gauze have also been tried. For example, the use of Blisterfilm (Medtronic, Minneapolis, MN, USA), a polyurethane adhesive film that has greater oxygen permeability, and Fixomull (BSN Medical, Inc., Charlotte, NC, USA), a stretchable hypo-allergenic adhesive dressing material, have been reported (136,137). However, their efficacy for the prevention of ESI has not been reported. A randomized controlled trial found that a silver ring mounted on PD catheter and placed at skin level did not reduce the incidence of ESI as compared with no treatment (138). Although chlorhexidine-impregnated dressings have been proved to be effective in preventing catheter-related infection for intravascular catheters (139), they have not been adequately evaluated in PD. In patients receiving no topical antimicrobial prophylaxis, about one-half of healthy exit sites are colonized with *S. aureus* (140). In these patients, trauma to the exit site may be treated with a short course of prophylactic oral antibiotics although there is no clinical trial to directly support this approach. It is a common practice to have appropriate protection for the catheter and exit site during bathing or swimming. However, there are no published data on this area.

OTHER ANTIMICROBIAL APPROACHES

- We suggest screening for nasal *S. aureus* carriage prior to PD catheter insertion **(2D)**.
- If nasal carriage of *S. aureus* is found in PD patients, we suggest treating by topical nasal application of mupirocin **(1B)**.

Nasal carriage of *S. aureus* is often regarded as a major risk factor of catheter-related infections. Although there is no good randomized study to support routine screening of nasal *S. aureus* carriage in PD patients, the efficacy of prophylactic intranasal antibiotics for the treatment of confirmed nasal carriage of *S. aureus* has been tested in several prospective studies. A randomized controlled trial found that intranasal mupirocin was more effective than nasal neomycin ointment for the elimination of *S. aureus* nasal colonization, but the background incidence of catheter-related infection was very low in this study (141). A prospective study showed that intranasal mupirocin reduced *S. aureus* ESI but not tunnel infection (142). In another small randomized controlled study, *S. aureus* grew less frequently from the exit site in the group randomized to intranasal sodium fusidate ointment (143). However, it is important to note that these studies only support the eradication of confirmed nasal *S. aureus* carriage; the benefit of routine screening, as well as the need of repeated screening after eradication, deserve further study.

One randomized controlled trial that compared cyclical oral rifampicin therapy (5 days every 3 months) with no treatment found significant reductions in catheter-related infection rate with rifampicin (144). In another randomized controlled trial involving pediatric PD patients who were nasal *S. aureus* carriers, a single course of oral rifampicin plus nasal bacitracin ointment also led to reduction in catheter-related infections (145). In another study, cyclic oral rifampicin and daily topical mupirocin to the exit site were equally effective in reducing the rate of catheter-related infections caused by *S. aureus* compared with historic control (107). However, adverse reactions to rifampicin were common (107). Drug interaction and rifampicin

resistance are also genuine concerns (146). The routine use of oral rifampicin for prophylactic purpose is not recommended.

Other oral antibiotics have also been tested. In a small randomized controlled study, oral ofloxacin did not reduce the incidence of *S. aureus* grown from catheter exit sites compared with no treatment (143). Two randomized controlled trials compared prophylactic treatment with oral cotrimoxazole (147) or cephalexin (148) with no treatment, but neither reported catheter-related infection as an outcome measure. The use of the staphylococcal vaccine was tested in a prospective multicenter placebo-controlled trial (149) that did not find any difference in the rate of catheter-related infection or peritonitis between the vaccine and control groups.

OTHER MODIFIABLE RISK FACTORS

Poor glycemic control is an important risk factor of catheter-related infections (150). Common clinical sense dictates that one should achieve a reasonable glycemic control in diabetic PD patients. One study reported that patients undergoing PD in an area of high air pollution and environmental particulate matter exposure had a higher infection rate than those with low exposure (151). It seems logical to advise patients to perform PD and exit-site care in a clean environment.

CONTINUOUS QUALITY IMPROVEMENT

There is a wide variation in adherence to guideline recommendations between PD units, which may contribute to the development of catheter-related infection and peritonitis (152). A Continuous Quality Improvement (CQI) program has been proposed for reducing infection in PD patients (18,153). The CQI team, usually including nephrologists, nurses, social workers, and dietitians, should hold regular meetings to examine all PD-related infections and identify the root cause of each episode. If a pattern of infections develops, the team should investigate and plan interventions to rectify the problem. Observational data suggest that CQI programs reduce peritonitis rates and improve technique survival (17,153–155). However, none of these studies reported catheter-related infection as an outcome measure.

MANAGEMENT OF CATHETER-RELATED INFECTIONS

Exit-site and tunnel infections may be caused by a variety of microorganisms. The most serious and common exit-site pathogens are *S. aureus* and *P. aeruginosa*, as these organisms frequently lead to peritonitis. Such infections must be treated aggressively (156–174). Coagulase-negative staphylococcal species and other bacteria (diphtheroids, streptococci, nontuberculous mycobacteria, and fungi) can also be involved.

CLINICAL PRESENTATION AND ASSESSMENT

As mentioned above, ESI is diagnosed by the presence of purulent drainage, with or without erythema of the skin at the catheter-epidermal interface. Tunnel infection typically presents as erythema, edema, induration or tenderness over the subcutaneous pathway, and usually occurs in the presence of ESI. Peri-catheter erythema without purulent drainage is sometimes an early sign of ESI but can also be a local skin reaction (e.g. recently placed catheter or after trauma). On the other hand, a positive culture without erythema and discharge probably indicates colonization but not infection. The scoring system described in Table 2 is sometimes recommended for the monitoring of exit sites (175). However, this system was developed by pediatricians and has not been formally validated in adult patients.

Some patients with clinical features of ESI alone actually have occult infection of the catheter tunnel and internal cuff, which may be revealed by sonography (15,176–178), and the presence of occult tunnel involvement predicts subsequent catheter loss (177). Possible indications for ultrasonographic examination of catheter tunnel are summarized in Table 3. However, there are few data to suggest how treatment should be tailored following ultrasound study.

MICROBIOLOGICAL INVESTIGATIONS

Many organisms can cause exit-site and tunnel infections, including microorganisms belonging to the normal skin flora, such as *Corynebacteria* (6,19). Microbiological examination should preferably include a combination of microscopy with aerobic and anaerobic culture. The Gram stain of exit-site drainage and microbiological culture findings may not be immediately

TABLE 2
Exit-Site Scoring System[a]

	0 point	1 point	2 points
swelling	no	<0.5 cm	>0.5 cm[b]
crust	no	<0.5 cm	>0.5 cm
redness	no	<0.5 cm	>0.5 cm
pain	no	slight	severe
drainage	no	serous	purulent

[a] Modified from Schaefer F *et al.* (175).
[b] Or involve tunnel.

TABLE 3
Possible Indications for Ultrasonographic Examination of Catheter Tunnel

- Initial evaluation of suspected tunnel infection, e.g. tunnel swelling without erythema and tenderness.
- Initial evaluation of exit-site infection without clinical features of tunnel involvement (especially if caused by *S. aureus*) (15,81,177)
- Follow-up of exit-site and tunnel infection after antibiotic treatment (168,172)
- Relapsing peritonitis episodes (178)

available but may help to guide the subsequent therapy. Cultures should be taken to the laboratory using transport materials that allow anaerobic bacteria to survive. Sensitivity testing is important in determining antibiotic therapy.

EXIT-SITE CARE

- We recommend that exit sites be cleansed at least daily during exit-site infection **(1C)**.

It makes clinical sense to continue with the usual exit-site care during catheter-related infections, and the committee suggests that the exit site be cleansed at least daily during ESI. For granulation tissue over the exit site without purulent discharge or tenderness, intensified local care or a local antibiotic cream is probably sufficient. However, there is no published trial on the efficacy of intensified exit care for the treatment (not prevention) of overt catheter-related infections. Topical antibacterial agents that have been tested for the prevention of catheter-related infections are summarized in Table 1. There are few data, however, on their efficacy in the treatment of active catheter-related infections. A recent study reported that topical ofloxacin solution is effective as an adjuvant to systemic antibiotics for the treatment of persistent exit-site and tunnel infection (179). The addition of topical gentamicin cream does not help to eradicate ESI caused by *Pseudomonas* species (180). Acetic acid (vinegar) has been used as a wound antiseptic and has been recommended for treatment of *Pseudomonas* wounds infections (181). However, the experience of acetic acid for the treatment of ESI in PD patients is limited.

EMPIRICAL ANTIBIOTIC TREATMENT

- We recommend empiric oral antibiotic treatment of exit-site infections with appropriate *S. aureus* cover such as a penicillinase-resistant penicillin (e.g. dicloxacillin or flucloxacillin) or first-generation cephalosporin, unless the patient has had a prior history of infection or colonization with methicillin-resistant *S. aureus* (MRSA) or *Pseudomonas* species (in these cases they should receive a glycopeptide or clindamycin, or appropriate anti-pseudomonal antibiotic, respectively) **(1C)**.

Oral antibiotic therapy is convenient and has an extensive clinical experience on its efficacy. Empiric therapy should primarily cover *S. aureus*. If the patient has a history of *P. aeruginosa* ESI, empiric therapy should include an antibiotic that would cover this organism. The Gram stain of exit-site drainage may help to guide the subsequent antibiotic therapy. Dosing recommendations for frequently used oral antibiotics are shown in Table 4 (86,144,145,165,182–195). The presence of granulation tissue over the exit site without other features of infection does not require antibiotic treatment. Although anti-fungal prophylaxis (e.g. oral nystatin) is recommended for the prevention of secondary fungal peritonitis during antibiotic treatment of peritonitis, there is no study that directly supports the use of anti-fungal prophylaxis during treatment of catheter-related infections. However, 1 randomized controlled trial did report a lower risk of fungal peritonitis with nystatin prophylaxis whenever antibiotics were prescribed (196).

MODIFICATION OF ANTIBIOTIC REGIMEN

Gram-positive organisms should be treated with oral penicillinase-resistant (or broad-spectrum) penicillin or a first-generation cephalosporin. To prevent unnecessary exposure, vancomycin should be avoided in the routine treatment of gram-positive exit-site and tunnel infections but will be required for MRSA infections. Sulfamethoxazole-trimethoprim, linezolid, daptomycin, clindamycin, doxycycline, and minocycline are possible alternatives for the treatment of MRSA. In slowly resolving or severe *S. aureus* ESI, rifampicin has been advocated as an adjunct, although there is no prospective study to support this practice. Rifampicin should never be given as monotherapy. Potential interaction with other concurrent medications (e.g. antihypertensive agents) should also be considered during rifampicin treatment.

Exit-site infections caused by *Pseudomonas* species are particularly difficult to treat and often require prolonged therapy with 2 antibiotics. Oral fluoroquinolones are recommended as the first-line choice, but resistance may develop rapidly with fluoroquinolone monotherapy. If quinolones are given concomitantly with sevelamer, multivalent cations (e.g. calcium, iron, or zinc preparations), sucralfate, magnesium-aluminum antacids, or milk, chelation and reduced quinolone absorption may occur. Administration of the quinolone should therefore be separated from these drugs by at least 2 hours

TABLE 4
Oral Antibiotics Used in Catheter-Related Infections

Amoxicillin	250–500 mg BD (182)
Amoxicillin/clavulanate	875 mg/125 mg BD (183)
Cephalexin	500 mg BD to TID (86)
Ciprofloxacin	250 mg BD (164) or 500 mg daily (184)
Clarithromycin	500 mg loading, then 250 mg BD (165)
Clindamycin	300–450 mg TID (185)
Cloxacillin/flucloxacillin	500 mg QID (186)
Erythromycin	250 mg QID (187)
Fluconazole	oral 200 mg loading, then 50–100 mg daily (188)
Levofloxacin	300 mg daily (189)
Linezolid	300–450 mg BD (190–192)
Metronidazole	400 mg TID (193)
Moxifloxacin	400 mg daily (194)
Rifampicin	450 mg daily for BW <50 kg; 600 mg daily for BW ≥50 kg (144,145)
Trimethoprim/ sulfamethoxazole	80 mg/400 mg daily (8) to 160 mg/800 mg BD (195)

BD = two times per day; TID = three times per day; QID = four times per day; BW = body weight.

(with the quinolone administered first). For elderly and diabetic patients, Achilles tendonitis is an uncommon but well recognized complication of fluoroquinolone treatment. If resolution of the infection is slow or if there is recurrent *Pseudomonas* ESI, a second anti-pseudomonal drug, such as intraperitoneal (IP) aminoglycoside or ceftazidime, should be added. Generally speaking, tobramycin and amikacin are more active on *Pseudomonas* species than gentamicin. In recent years, catheter-related infections caused by *Burkholderia cepacia* (197,198) and non-tuberculous mycobacteria (199,200) have been increasingly reported, and their treatment should be individualized.

MONITORING AND DURATION OF THERAPY

- We recommend that exit-site infection, except episodes caused by *Pseudomonas* species, be treated with at least 2 weeks of effective antibiotics **(1C)**.
- We recommend that exit-site infection caused by *Pseudomonas* species and any tunnel infection be treated with at least 3 weeks of effective antibiotics **(1C)**.

Patients should be followed with the catheter tunnel and exit site examined in order to determine the clinical response to treatment. Photographic record (for example, by mobile phone) is increasingly used and probably valuable for serial monitoring. Antibiotic therapy should be continued until the exit site appears entirely normal. For ESI, effective antibiotic should be continued for at least 2 weeks. However, treatment for 3 weeks is recommended for tunnel infection or ESI caused by *Pseudomonas* species. Close follow-up is necessary to determine the response to therapy and relapse. Repeating exit-site wound swab for bacterial culture 1 to 2 weeks after the discontinuation of antibiotic treatment has been advocated for risk assessment (9), but there is no clinical trial on this area.

Ultrasonography of the catheter tunnel has been advocated for evaluating the response to therapy, and may be used to determine the need for surgical intervention (Table 3). One uncontrolled study reported that amongst patients with clinical ESI, ultrasonography of the exit site after finishing a course of antibiotic therapy had prognostic value (168). In this study, a sonolucent zone around the external cuff of over 1 mm thick following antibiotic treatment and the involvement of the proximal cuff were associated with poor clinical outcomes (168). In another uncontrolled study, patients who had a clinical tunnel infection caused by *S. aureus* and significant decline of the sonographic hypoechogenic area around the cuff after 2 weeks of antibiotic therapy did not require catheter removal, while no significant decline was observed in patients who later lost their catheters (172).

CATHETER REMOVAL AND REINSERTION

- We recommend simultaneous removal and reinsertion of the dialysis catheter with a new exit site under antibiotic coverage in PD patients with refractory exit-site or tunnel infection without peritonitis, defined as failure to respond after 3 weeks of effective antibiotic therapy **(1C)**.
- We suggest removal of the dialysis catheter in PD patients with exit-site infections that progress to, or occur simultaneously with, peritonitis **(2C)**.
- We suggest that, for patients who have undergone dialysis catheter removal for simultaneous exit-site or tunnel infection and peritonitis, any reinsertion of a PD catheter be performed at least 2 weeks after catheter removal and complete resolution of peritoneal symptoms **(2D)**.

The indications of catheter removal for catheter-related infections are summarized in Table 5. Patients with ESIs that progress to, or occur simultaneously with, peritonitis generally require catheter removal. Catheter removal should also be considered for isolated catheter-related infections (i.e. without peritonitis) if prolonged therapy with appropriate antibiotics (e.g. over 3 weeks) fails to resolve the infection.

For patients with simultaneous exit-site or tunnel infections and peritonitis, PD catheter removal should be followed by temporary hemodialysis with no attempted reinsertion of the PD catheter until at least 2 weeks after catheter removal and complete resolution of peritoneal symptoms. In the scenario of catheter infections, however, a few observational studies showed that simultaneous removal and reinsertion of the dialysis catheter with a new exit site under antibiotic coverage is effective in eradicating the infections (169–171,174,201,202). However, there is no controlled trial in this area.

OTHER CATHETER INTERVENTIONS

In addition to catheter removal, a number of interventions have been tried for the treatment of chronic or refractory catheter infections. A few observational studies reported that cuff-shaving is a reasonable alternative to catheter replacement for persistent tunnel infection (173,203,204). The un-roofing technique, with or without *en bloc* resection of the skin and tissues around the peripheral cuff, has been advocated but is associated with considerable risk of peritonitis (203–207). In contrast, observational data suggest that partial catheter re-implantation (200) and catheter diversion procedure with exit-site renewal (208–213) could be considered for catheter salvage. The latter technique has been extensively reported as an alternative to catheter removal for refractory exit-site

TABLE 5
Possible Indications for Catheter Removal in Catheter-Related Infections

- Catheter infections that occur simultaneously with peritonitis episodes
- Catheter infections that lead to subsequent peritonitis episodes
- Refractory catheter infections*

* Defined as failure to respond after 3 weeks of effective antibiotic therapy; simultaneous catheter reinsertion could be considered.

or tunnel infections, although no randomized controlled trial has been completed. The precise methods for this strategy have been described in detail previously (205,210,213,214).

FUTURE RESEARCH

Clinical trials are required on the primary and secondary prevention of catheter-related infections. Specifically, the optimal method of exit-site care and the critical components of a good patient-training program remain to be defined. Further studies are also needed to assess the efficacy and safety of various treatment regimens, as well as the optimal duration of treatment. The biology and management of catheter biofilm is another area to be explored.

DISCLOSURES

CCS receives a research grant and consultancy fees from Baxter Healthcare. DWJ has received consultancy fees, research grants, speaker's honoraria and travel sponsorships from Baxter Healthcare and Fresenius Medical Care. JB serves as a consultant for Baxter Healthcare. AEF received travel grants and a speaker honorarium from Baxter Healthcare. YI received research grants or speaker honoraria from Baxter, Terumo, JMS, Chugai, Kirin, Eisai, and Kissei pharmaceutical companies. RK has previously received fees for invited lectures from Baxter. TM receives a speaker honorarium, consultant fees, and travel grant from Baxter. SVE receives speaker's fees from Baxter. EAB receives research funding and speaker honoraria from Baxter Healthcare and speaker honoraria from Fresenius Medical Care. The others declare no conflict of interest.

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