

Exit Site Infections: Systematic Microbiologic and Quality Control Are Needed

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For the period January 2005 to June 2008, we reviewed the rates, causes, and outcomes of exit-site infection (ESI) among 137 consecutive patients [mean age: 51 ± 16 years; 17 (12.4%) with diabetes; 76 (55%) on automated PD; time at risk: 240.41 dialysis years; mean follow-up: 20.4 ± 13.8 months]. Treatment protocol included mini-laparotomy and Popovich–Moncrief placement method, with pre-surgical cefazolin prophylaxis and routine prescription of topical mupirocin for the exit site. Oral cotrimoxazole was the initial empirical ESI treatment.

A total of 49 patients (36%) experienced 76 episodes of ESI, for a global incidence of 0.31 episodes per year at risk. Gram-positive organisms occurred in 56% of the cases, and gram-negative organisms in 27%. Staphylococcus aureus caused 15 ESIs (0.06 episodes/patient–year), and only 15% of gram-positive organisms were methicillin resistant. Methicillin-resistant S. aureus were all sensitive to cotrimoxazole. Pseudomonas species caused 11 ESIs (0.04 episodes/patient–year). Other Enterobacteriaceae occurred at a rate of 0.03 episodes/patient–year. Fungal ESIs occurred at a rate of 0.004 episodes/patient–year. The ESI cure rate was 96%. In 3 patients, the catheter was removed, but only 2 patients (2.6%) experienced ESI-related peritonitis.

Our unit's treatment policy and prophylactic use of exit-site mupirocin resulted in a low S. aureus ESI rate without an alarming incidence of gram-negative or Pseudomonas infections. Routine microbiologic and quality control is mandatory for strategies individualized to the dialysis center.

Key words

Exit-site infection

Introduction

Peritoneal dialysis (PD) is being applied in an increasing number of patients, proving its efficacy and, in several respects, its many advantages as a first modality of renal replacement therapy in uremic patients. However, despite major technique advances and cumulative experience, access-related infections are still a major cause of technique dropout and transfer to hemodialysis. Exit-site infection (ESI) in the immediate post-catheter implantation period may depend on surgical procedures, bacterial colonization, and trauma. Later ESIs occur almost unpredictably, possibly related to mechanical irritation, hypersensitivity to silicone rubber, hyperhydrosis, or reduced tissue reactivity (1). The infection can migrate to the outer and inner cuffs, spread to the peritoneal cavity, and lead to tunnel infection, peritonitis, and even catheter loss.

During the 1990s, the overall probability of developing an ESI was 33% – 46% at 1 year and 59% – 70% at 3 years on continuous ambulatory PD (CAPD). Peritonitis induced by an ESI is found in 30% – 50% of patients, and catheter loss may be as high as 15% – 57% (2,3). Systematic reviews demonstrated that the method of implantation, type of catheter, specific exit-site care protocol, and mode of dialysis [CAPD, automated PD (APD)] did not significantly influence peritonitis or ESI rates (4). But mupirocin prophylaxis led to a 63% reduction in the risk of infection with *Staphylococcus aureus*, with peritonitis being reduced by 66% and ESIs by 62% (5). Systematic review is nevertheless mandatory to verify the microbiologic trends and sensitivities in each unit. A standardized rate report is also useful for comparisons with the experience of other centers.

We evaluated the incidence, type, and natural course of ESI in 137 patients undergoing CAPD or continuous cycling PD at Hospital Geral de Santo

Antônio between January 2005 and June 2008. The focus was on quality control, analyzing rates of infection with specific microbiologic agents (*S. aureus*, *Pseudomonas aeruginosa*, other *Enterobacteriaceae*), and outcomes.

Patients and methods

Our retrospective study of ESI incidence, causes, microbiologic sensitivities, and cure rates was performed in a single-center university hospital PD unit for the period between 1 January 2005 and 30 June 2008. During that time, 137 consecutive patients [white adults; 90 (66%) women; mean age: 51 ± 16 years (range: 21 – 88 years); 17 (12.4%) with diabetes; 76 (55%) on APD; time at risk: 240.41 dialysis years] were treated. Mean follow-up was 20.4 ± 13.8 months, and 76 ESI episodes occurred.

Implantation protocol

In all patients, double-cuffed Tenckhoff catheters were placed by an expert team of nephrologist and surgeon using mini-laparotomy and the Moncrief–Popovich method, in an operating room under sterile conditions. Nasal mupirocin was prescribed as part of the pre-implantation protocol in nasal carriers of *S. aureus*. A break-in period of more than 4 weeks before exteriorization of the external segment of catheter was standard, usually extended to additional months until dialysis was needed. All patients received prophylactic antibiotics (intravenous cefazolin 1 g) on implantation and on exteriorization of the external segment of the catheter.

Exit-site care

After exteriorization of the catheter's external segment, patients were taught to clean the exit site every day with saline solution (0.9% NaCl) and to keep it dry. They were prescribed 2% mupirocin cream to be used at the exit site once daily.

Exit-site infection

At each clinic visit, an expert nurse classified the exit site as “infected,” “equivocal,” or “good” according to a classification adapted from Twardowski (6). A diagnosis of ESI was made whenever clinical signs of infection led to an exit-site swab and a positive culture.

Equivocal exits were kept under surveillance, with topical antibiotic, saline soak, or silver nitrate

granuloma cauterization. Exits that did not improve within 1 month were classified as “infected,” and a systemic oral antibiotic was prescribed.

The first choice of empiric antibiotic was cotrimoxazole, usually taken for 2 weeks or until a week had passed since the cessation of signs of ESI. Once a culture report became available, the patient was switched to an appropriate antibiotic (if necessary). *Pseudomonas* ESIs were treated with two antipseudomonal antibiotics: oral ciprofloxacin and intraperitoneal ceftazidime. Slow-responding *S. aureus* ESIs were treated with the addition of oral rifampicin. Prophylaxis against fungal peritonitis was undertaken by adding oral fluconazole in cases of recurrent or prolonged antibiotic prescriptions for ESI.

A recurrence of ESI caused by the same organism 30 days or more after appropriate therapy was considered a chronic ESI (7). The presence of peritonitis caused by the same organism or by a fungus within 1 month after diagnosis of an ESI was considered an ESI-related peritonitis.

If prolonged therapy with appropriate antibiotics failed to resolve the infection, external cuff shaving was performed. The peritoneal catheter was removed after unsuccessful cuff shaving in patients with persistent chronic ESI, when the ESI progressed to peritonitis, or when ESI occurred in conjunction with a peritonitis caused by the same infectious agent (with the exception of coagulase-negative *Staphylococcus*). Catheter removal was considered to be related to ESI if it was performed within 3 months after the ESI diagnosis.

Statistical analysis

The statistical analysis was performed using SPSS version 15.0 for Windows (SPSS, Chicago, IL, U.S.A.). Using the chi-square test, *p* values below 0.05 were considered significant.

Results

Of the 137 patients studied (240.41 dialysis years at risk), 49 (36%) experienced 76 ESIs, for a global ESI incidence rate of 0.31 episodes per year at risk. Of the 76 episodes, 71 (93.4%) were acute, and 5 (6.6%) were chronic. The mean number of ESI episodes per patient was 1.62 ± 0.96 (range: 1 – 5 episodes); 69.4% of patients had 1 ESI episode, 8.2% had 2 episodes, 18.4% had 3 episodes, and 4.0% had more than 3 episodes.

Gram-positive organisms were present in 56% of the cases, and gram-negative organisms in 27%. *S. aureus* was the most frequent infectious agent, followed by *P. aeruginosa*, *Enterobacteriaceae*, and *Corynebacterium* (Table I). *S. aureus* caused 15 ESIs, for a rate of 0.06 episodes/patient-year. Only 15% of gram-positive agents were methicillin resistant. All cases of methicillin-resistant *S. aureus* were sensitive to cotrimoxazole. *Pseudomonas* species caused 11 ESIs, for a rate of 0.04 episodes/patient-year, and 82% of cases were sensitive to ciprofloxacin. Other *Enterobacteriaceae* occurred at a rate of 0.03 episodes/patient-year. Fungal ESI occurred in only 1 case (1.3%; Tables I and II).

Neither age ($\chi^2 p = 0.14$), diabetes status ($\chi^2 p = 0.53$), nor dialysis modality (APD: $\chi^2 p = 0.13$) was more frequently associated with ESIs.

In 5 ESI episodes (isolated agents were 1 *Pseudomonas*, 1 *Proteus*, 3 *Corynebacterium* species), external cuff shaving was followed by cure. In 3 patients, the catheter was removed and a transfer made to hemodialysis, but only 2 of these patients (2.6%) experienced ESI-related peritonitis: one experienced a fungal ESI without peritonitis, another experienced ESI and peritonitis caused by *Streptococcus* species, and a third developed a tunnel infection and peritonitis caused by *S. aureus*. The ESI cure rate was 96%.

Discussion

ESI registry

Skin infection at the catheter exit site remains a relevant problem in PD patients. Peritonitis episodes are usually easily identified and counted, but exit sites

vary broadly in appearance from uninfected to infected, making for a wide variation in ESI classification and treatment between PD units (3). This variation leads to imprecise definitions of ESI, inconsistent monitoring, and difficulties in interpreting study results. In trying to avoid these difficulties, we considered ESI only when signs of infection were present and cultures were available. The difficulty in microbiologic ESI diagnosis is highlighted in that regional commensal flora are often reported in clinically evident ESIs.

Agents and incidence rates

Imprecise definitions of ESI and variation in the way that new episodes of infection are described make it difficult to compare study results. Many trials report ESI for a specific agent as a percentage of the total. However, if the incidence of a specific organism is reduced, the proportion of ESIs caused by other agents will increase, without an increase in absolute numbers (5). A way to overcome this limitation is, as proposed by Piraino *et al.*, to report results as incidence rates—that is, number of infections by a specific organism divided by time at risk (5).

In adults, previously reported ESI rates range from 0.05 – 1.02 episodes/patient-year (3,8). Gram-positive agents were responsible for most pericatheter infectious episodes, and *S. aureus* (at a rate of 0.46 per dialysis year at risk) was the primary cause of ESIs (3,5). *P. aeruginosa* was the most frequent gram-negative agent (8% – 12%), followed by other *Enterobacteriaceae* (7% – 14%) (3,9).

Our rate data compare favorably with those from a recent reference center report (Table II).

Prophylaxis strategies

Many strategies have been developed to reduce catheter-associated infections, but widely variable exit-site management protocols are used and are variably efficient (10). Against expectations, implantation technique (including the Popovich–Moncrief method) did not prove to reduce ESIs (4). Perioperative intravenous antibiotics significantly reduced the risk of early peritonitis, but not exit-site and tunnel infections (11).

Carriage of *S. aureus* has been recognized as a risk factor for ESIs and peritonitis in PD patients (5). Our policy of treating *S. aureus* carriers is therefore advisable. However, besides the nose, *S. aureus*

TABLE I Micro-organisms responsible for exit-site infections (ESIs)

Micro-organisms	ESIs (n=76)	
	(n)	(%)
Regional commensal flora	17	22.3
<i>Staphylococcus aureus</i>	15	19.7
<i>Pseudomonas</i> spp.	11	14.4
<i>Enterobacteriaceae</i>	9	11.8
<i>Corynebacterium</i>	8	10.5
Polymicrobial flora	7	9.2
Other <i>Staphylococcus</i>	4	5.2
<i>Streptococcus</i> spp.	4	5.2
Fungus	1	1.3

TABLE II Exit-site infection (ESI) rates

Micro-organism	ESI rate (episodes/patient-year)	
	Santo Antonio Hospital ^a	Pittsburgh Dialysis Registry ^b
<i>Staphylococcus aureus</i>	0.06	0.04
Other gram-positive	0.05	0.05
<i>Pseudomonas</i> spp.	0.04	0.06
<i>Enterobacteriaceae</i>	0.03	—
Other/gram-negative	—	0.005
Fungus	0.004	0.01
Polymicrobial flora	0.02	0.01
Commensal flora	0.07	—
Sterile or no culture	—	0.014
TOTAL	0.31	0.19

^a Time at risk: 240.41 dialysis years.

^b Time at risk: 213.54 dialysis years.

can also colonize skin, nails, the exit-site orifice, and the hands of partners or PD center personnel; all patients are therefore at risk for acquiring it (5). Eradication by applying nasal or exit-site mupirocin significantly reduces overall ESIs to 0.29 episodes per dialysis-year at risk, and *S. aureus* ESIs to 0.12 episodes per dialysis-year at risk (11). No randomized controlled trials have compared intranasal with exit-site mupirocin, and it is not clear if nasal mupirocin prevents colonization at other sites (5). A limitation of our study is that patients were not stratified by nasal *S. aureus* carriage status. However, daily mupirocin application to the exit site in all patients is intended to avoid the problem of colonization of locales other than the nose, intermittent carriage, and acquisition of *S. aureus* between visits (5).

Even though antibiotic prophylaxis of ESIs with mupirocin might induce bacterial resistance and a change in bacterial profile (8)—and also that resistance could be more likely to occur with intermittent application of exit-site mupirocin (12)—its application is recommended if reduction of the *S. aureus* infection rate is a goal. The widespread use of mupirocin at the exit site, with eradication of gram-positive agents, led to the fear of an increase in gram-negative ESIs, namely *P. aeruginosa*. Once *S. aureus* infections are reduced, the proportion of ESIs attributable to other (gram-negative) agents will increase. This percentage increase is misleading. When ESI rates are compared, no evidence of an increase in catheter infections by gram-negative agents in patients under mupirocin prophylaxis is observed (5).

When compared with mupirocin, daily application of gentamicin to the exit site resulted in a 57% reduction in ESIs (including those caused by *P. aeruginosa* and *S. aureus*) and a 35% reduction in peritonitis; however, this protocol was associated with an increase in fungal ESIs (5,13). Some PD units have elected to use gentamicin as their first option for ESI prophylaxis. In our unit, mupirocin was chosen as the first option for prophylaxis because it seemed better not to use the same antibiotic for prophylaxis and treatment, because aminoglycosides need to be preserved to treat emerging multiresistant organisms, and because there was concern that gentamicin, a broad-spectrum antibiotic, could lead to an increase in fungal infections. Once an infection registry and quality control are in place, strategies individualized to the center are legitimate.

When we compare ESI rates from our unit with those reported from units in which patients are under prophylaxis with gentamicin (5), results with narrower-spectrum antibiotic prophylaxis were similar (5), and the rate of fungal ESIs was lower (Table II).

Predisposing factors

In our study, ESIs were not more frequent in elderly, diabetic, or APD patients. Except for *S. aureus* carriage, other risk factors for ESIs are inconsistently documented. Previous studies have reported that age and longer dialysis duration were not associated with an increase in ESIs (14,15), but African American and prior renal transplant patients have an increased susceptibility to catheter-related infections (5,14). Diabetic and immunosuppressed patients are also at

risk for early *S. aureus* ESIs (5). Patients on APD were found to have lower rates of peritonitis, but not lower rates of ESIs or tunnel infections (16).

Chronic ESIs and long-term complications

Chronic ESIs represent 6.8% – 11.8% of all ESIs, and chronic infections are most frequently caused by *S. aureus* and *P. aeruginosa* (17,18), predisposing to peritonitis (5). In our experience, *Corynebacterium* was also a cause of morbidity. But our low number of chronic ESIs and high cure rate are also a result of our policy of external cuff shaving in persistent unresponsiveness of ESIs to antibiotics. This procedure can resolve 77% – 88% of chronic ESIs, without dialysate leakage or catheter laceration (17,18). In our report, a 100% cure rate was obtained with external cuff shaving.

Catheter removal is needed in 15% – 57% of catheter-related infections (2,3). Patients with pseudomonal, anaerobic, fungal, and polymicrobial peritonitis are at high risk of catheter loss (19). We found an excellent ESI cure rate of 96%, with a low rate of catheter loss (2.6%).

Conclusions

Protocols to reduce the infection risk in PD patients include careful catheter placement, patient training, exit-site care with *S. aureus* prophylaxis, prevention of procedure-related and fungal peritonitis, and good management of infectious episodes. Our unit treatment policy and prophylactic exit-site mupirocin led to a low *S. aureus* ESI rate without an alarming incidence of gram-negative or *Pseudomonas* infections.

Continuous monitoring of infection protocols, together with routine microbiologic assessment and quality control, is mandatory for strategies individualized to a center.

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