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Dialysis

ORIGINAL ARTICLE

Pseudomonas exit-site infection: treatment outcomes with topical gentamicin in addition to systemic antibiotics

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Abstract

Background: Although, *Pseudomonas* exit-site infection (ESI) is recognized as a major complication of peritoneal dialysis (PD) with high risk of catheter loss due to refractory/recurrent infection or peritonitis, there is remarkably little literature about treatment outcomes. International Society for Peritoneal Dialysis guidelines advise the use of one to two antibiotics; in addition, we change standard exit-site care by stopping prophylactic mupirocin and starting regular use of gentamicin 1% cream.

Methods: Retrospective review of outcomes of *Pseudomonas* ESI from January 2012 to March 2015.

Results: During the study period, a total of 135 patients were on PD with an overall incidence of any ESI of 0.36/patient-year. There were 14 patients with ESI episodes with *Pseudomonas* with a rate of 0.12/patient-year. In total, 13 of 14 patients with ESI episodes were treated with oral ciprofloxacin and/or intraperitoneal (IP) gentamicin or ceftazidime, plus topical gentamicin, with a success rate of 38% (5/13). One patient had gentamicin-resistant *Pseudomonas* species and was treated successfully with topical polymyxin/bacitracin cream. Median follow-up time in cured patients was 385 days (range 74–1107). Six patients had associated with *Pseudomonas* peritonitis, four during follow-up and two at initial presentation. Three patients had recurrent ESI with *Pseudomonas*, with one successfully re-treated with topical and IP gentamicin. In total, in only 50% of the patients was *Pseudomonas* ESI successfully treated. Five of the patients (36%) changed modality to permanent haemodialysis following catheter removal.

Conclusion: Eradication of *Pseudomonas* ESI remains difficult even with the addition of topical gentamicin to the exit site. There should be a low threshold for catheter replacement.

Key words: exit-site infections, peritoneal dialysis, *Pseudomonas aeruginosa*, topical gentamicin

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Introduction

Catheter-related infection, including exit-site infection (ESI), tunnel infection and peritonitis, remains one of the most important complications of peritoneal dialysis (PD) and is one of the leading causes of PD failure. ESI is a known risk factor for subsequent tunnel infection as well as for peritonitis. Therefore, prevention of ESI is crucial for the long-term outcome of PD patients. The most commonly used prophylaxis for ESI is mupirocin, an antibacterial ointment against Gram-positive organisms, which account for ~75% of ESIs. Several studies have shown a significant reduction of ESI rate with Gram-positive organism with the use of topical mupirocin, but an unchanged rate of ESI with Gram-negative organisms including *Pseudomonas* [1]. ESI with *Pseudomonas* is recognized as a major complication of PD, with high risk of catheter loss due to refractory/recurrent infection or peritonitis. There is remarkably little literature about treatment outcomes in patients with *Pseudomonas* ESI and there is no standard treatment protocol. The reported cure rate of *Pseudomonas* ESI with different systemic antibiotic treatment regimens ranges from 42 to 83% [2–4]. International Society for Peritoneal Dialysis guidelines advise the use of one to two systemic antibiotics in case of *Pseudomonas* ESI [5]. There are no data or recommendations about any topical treatment of *Pseudomonas* ESI. Bernardini *et al.* [6] showed that topical prophylaxis at the exit site with gentamicin results in an equal reduction of ESI with Gram-positive organisms compared with mupirocin and also a reduction in ESI with Gram-negative organisms including *Pseudomonas* [6]. Since publication of this paper, we have managed patients with *Pseudomonas* ESI by changing their prophylactic exit-site care from mupirocin to gentamicin 1% cream in addition to the recommended treatment with one to two systemic antibiotics. Whether this additional use of topical gentamicin cream to systemic antibiotic treatment in *Pseudomonas* ESI will enhance the cure rate is unknown. We have therefore retrospectively analysed the outcomes of these patients at our centre.

Materials and methods

This is a single-centre retrospective review of the outcomes of *Pseudomonas* ESI in PD patients from January 2012 to March 2015 at the Imperial College Renal and Transplant Centre, Hammersmith Hospital, London. All the patients had used prophylactic topical mupirocin at their exit sites, which were clinically monitored for signs of infection at their regular clinic visits (every 6–8 weeks). ESIs were defined by the presence of pericatheter erythema, tenderness and purulent drainage and were attributed to *Pseudomonas* in association with a positive exit-site culture for *Pseudomonas*. Resolution of the ESI was defined by the absence of any clinical signs for ESI and a negative culture. In case of *Pseudomonas* ESI, systemic antibiotic treatment with oral ciprofloxacin monotherapy or in combination with intraperitoneal (IP) gentamicin or ceftazidime was given for at least 14 days and the prophylactic topical mupirocin was changed to regular topical gentamicin 1% cream. Patients were advised to take ciprofloxacin at least 2–4 h apart from any phosphate binders.

Results

During the study period, a total of 135 patients were on PD, with an overall incidence of any ESI of 0.36/patient-year. There were 14 patients with ESI episodes due to *Pseudomonas*, with a rate of 0.12 per patient-year. There were equal numbers of male ($n = 7$) and female ($n = 7$) patients with a median age of 57 years (range 25–80) and a median time to first ESI episode of 426 days (range 18–1718). Sensitivities of *Pseudomonas* were available in 13 of 14 patients. Only one patient had a gentamicin-resistant *Pseudomonas* species. Treatments and outcomes are summarized in Figure 1. The median follow-up time in cured patients was 373 days (range 74–1107). Six patients had associated *Pseudomonas* peritonitis, four during follow-up and two at initial presentation. The median time to *Pseudomonas* peritonitis was 140 days (range 91–315) after the initial ESI. Four of these episodes resulted in catheter removal. The catheter was removed in another three patients because of the severity or recurrence of the ESI. Only two of the seven patients requiring catheter removal returned to PD. Only six patients had an apparent cure of their *Pseudomonas* ESI, with no recurrence or subsequent peritonitis.

Discussion

Our retrospective analysis suggests that there is no additional benefit of topical gentamicin cream used in conjunction with systemic antibiotics in patients with *Pseudomonas* ESI. The overall cure rate of 50% in our population was similar to previously reported cure rates [3,4]. There are probably several factors that contribute to the low efficacy of topical gentamicin in *Pseudomonas* ESI compared with its ability to prevent *Pseudomonas* ESI. First, *Pseudomonas* is known to have the ability to form biofilm; it is very likely that this happens with ESI and the biofilm formed lowers the efficacy of topical gentamicin [7]. In addition, the inoculum of *Pseudomonas* in ESI might be too high and the local gentamicin concentration too low to reach the needed minimal inhibitory concentration of the drug. We did not systematically perform tunnel sonography in our patients, so there is a risk of missed clinically not apparent tunnel infections. These would not respond to any topical treatment since the drug is not delivered along the catheter to the infection site. One patient with gentamicin-resistant *Pseudomonas* was successfully treated with topical polymyxin/bacitracin ointment, but this was complicated by a subsequent fungal infection, which is well recognized when using this broadspectrum ointment [8].

We observed recurrent *Pseudomonas* ESI despite further prophylactic treatment with topical gentamicin after the first episode in three patients. Although there is concern about gentamicin resistance developing in patients with prophylactic topical treatment [9], all the *Pseudomonas* species in these three patients remained susceptible to gentamicin. The three patients had been initially successfully treated with oral ciprofloxacin monotherapy. One patient had a ciprofloxacin-resistant *Pseudomonas* species at the time of recurrence. Development of ciprofloxacin resistance during treatment was also seen in a patient with an unresolved *Pseudomonas* ESI with ciprofloxacin monotherapy. The development of ciprofloxacin resistance in *Pseudomonas* infection treated with ciprofloxacin monotherapy is well known [10]. Long-term successful treatment of *Pseudomonas* ESI with oral ciprofloxacin monotherapy was seen in only 4/10 (40%) of our patients. This is in contrast to the study of Kazmi *et al.* [2] with an overall cure rate of 15/18 (83%) of *Pseudomonas* ESI episodes in 17 patients with oral ciprofloxacin monotherapy. But when taking into account the *Pseudomonas* peritonitis in 4 patients during follow-up, only 11/17 patients (65%) showed long-term cure in their study. The association of ESI with concurrent or later peritonitis with the same species is well known and was observed in six patients, of whom only one was successfully treated with IP gentamicin and without replacement or removal

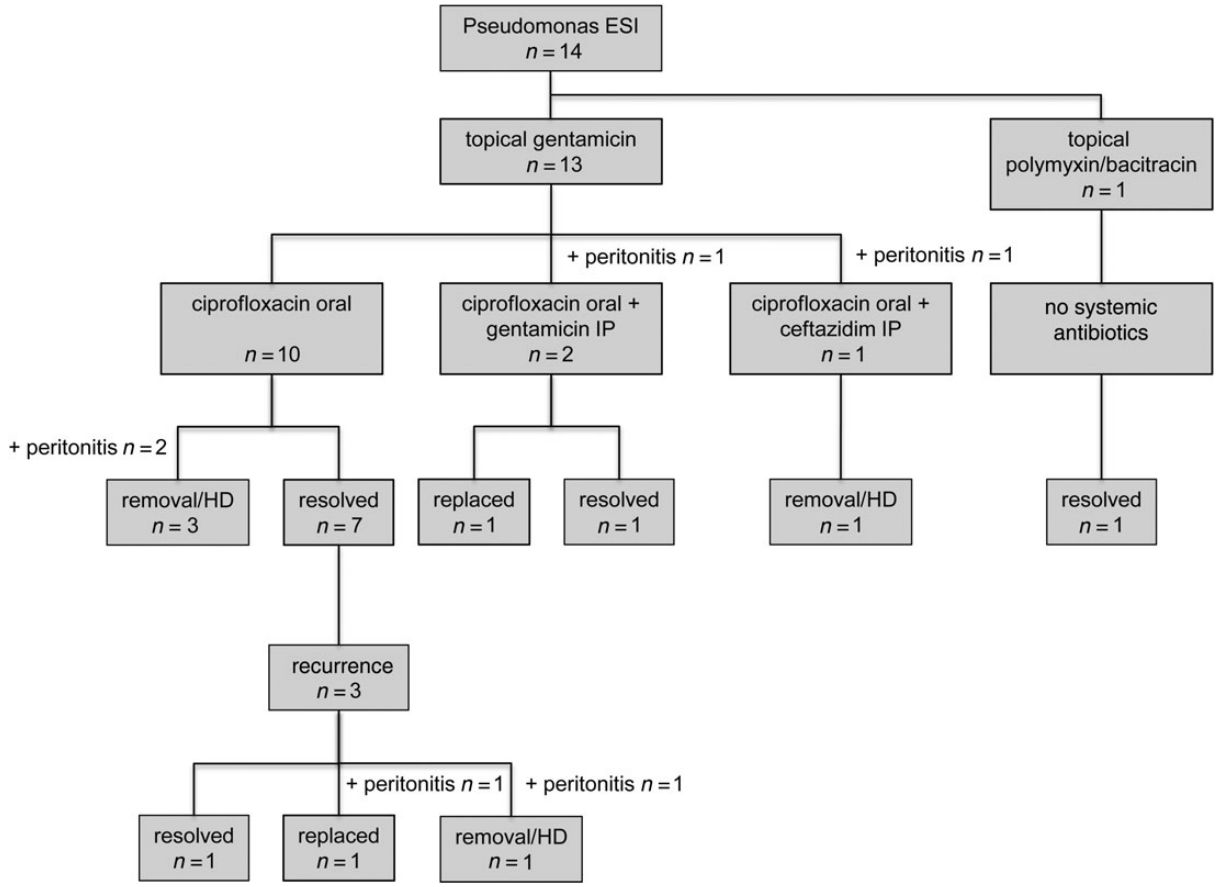

Fig. 1. Treatment outcome of patients with *Pseudomonas* ESI.

of the catheter. In total, in only 50% of the patients was *Pseudomonas* ESI successfully treated. This study confirms that *Pseudomonas* ESI is an important cause of PD technique failure. Five of the patients (36%) changed modality to permanent haemodialysis following catheter removal. Whether an initial treatment with two systemic antibiotics would lead to better outcomes has not been well investigated. However, two of three patients in our study initially treated with two systemic antibiotics had concurrent *Pseudomonas* peritonitis and failed treatment.

There are some limitations of our study. It is a retrospective observational study and we therefore do not have a control group without the use of topical gentamicin cream. So there might still be an additional benefit of topical gentamicin in *Pseudomonas* ESI. However, considering the overall very low cure rate in our study, which is comparable with the available data in the literature, any therapeutic effect of topical gentamicin is very unlikely. Another limitation is the small number of patients in the study. However, due to the very low incidence of *Pseudomonas* ESI, it is naturally very difficult to perform a properly powered prospective controlled trial to study the impact of topical gentamicin. In addition, our study is, to our knowledge, the first study that analysed the effect of topical gentamicin in *Pseudomonas* ESI.

In conclusion, eradication of *Pseudomonas* ESI remains difficult even with the addition of topical gentamicin to the exit site. The ideal systemic antibiotic treatment is still to be determined. There should be a low threshold for catheter replacement in case of unresolved infection, as the risk of occurrence of *Pseudomonas* peritonitis is high.

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Conflict of interest statement

E.B. has received speaker honoraria and research funding from Baxter Healthcare. The results of this study have not been published in a paper previously in whole or part.

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