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Review

Stenotrophomonas maltophilia: an emerging pathogen in dialysis units

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Infection is an important cause of morbidity and mortality among patients with end stage renal disease. *Stenotrophomonas maltophilia* is an unusual yet emerging pathogen in dialysis units. We performed a systematic PubMed/Medline and Scopus review of peer-reviewed English papers on *S. maltophilia* infections among patients undergoing chronic dialysis, with regard to vascular accesses, systemic infections and environment contaminations. Moreover, we suggest a treatment algorithm to preserve the patient and the permanent dialysis catheters.

Introduction

Stenotrophomonas maltophilia is an aerobic, non-fermentative, motile, Gram-negative bacterium, which was initially classified as *Pseudomonas maltophilia*. *S. maltophilia* was initially grouped in the genus *Xanthomonas* and then the genus *Stenotrophomonas* in 1993 (Palleroni & Bradbury, 1993). It propagates in moist environments (water, medical equipment, soil and sewage) and colonizes medical devices (Marshall *et al.*, 1989; Passerini de Rossi *et al.*, 2007).

S. maltophilia is becoming a relevant opportunistic pathogen, causing bacteraemia, pneumonia, and intra-abdominal and mucocutaneous infections; subjects at higher risk of *S. maltophilia* infection are debilitated, immunosuppressed and neutropenic patients (Looney *et al.*, 2009; Brooke, 2012; Samonis *et al.*, 2012). Dialysed patients are an ideal target for infections: they are immunosuppressed because of uraemia, old age, malnutrition, comorbidities and the increased use of artificial accesses such as prosthetic grafts, central venous or peritoneal catheters.

The treatment of *S. maltophilia* infections can become cumbersome because the pathogen harbours an intrinsic resistance to several classes of antibiotics, through beta-lactamase production, drug efflux pumps and decreased permeability, and this resistance might also emerge during the course of therapy (Garrison *et al.*, 1996; Vila & Marco, 2002). Most *S. maltophilia* strains are in general resistant to extended-spectrum penicillin, third-generation cephalosporins and carbapenems (Pankuch *et al.*, 1994; Vartivarian *et al.*, 1994), but sensitive to the newest generation of quinolones, aminoglycosides and trimethoprim/sulfamethoxazole (Nicodemo & Paez, 2007; Samonis *et al.*, 2012).

Here, we review the available literature about *S. maltophilia*-related infections in patients undergoing either extracorporeal or peritoneal dialysis.

Methods

We conducted a systematic PubMed/Medline and Scopus review of peer-reviewed papers on *S. maltophilia* infections among adult patients undergoing chronic dialysis. Search terms used were: '*Stenotrophomonas maltophilia*' and 'dialysis'. We found 24 and 17 articles in PubMed/Medline and Scopus respectively, but after a cross-matching and retrieving results specific for adult chronic dialysis patients and papers written in English, we were left with 17 papers (Table 1). Finally, we performed a summary of the literature with regard to the dialysis access outcome (Table 2).

Results

Only one study has been published on the role of *S. maltophilia* colonization in dialysis units. In a Greek multicentre study on the colonization of municipal water supplies, treated water and dialysate, *S. maltophilia* accounted for 13.5 % of isolates, just after *Pseudomonas* (22.7 %) and *Chryseobacterium* (14.9 %) (Arvanitidou *et al.*, 2003). Earlier reports described *S. maltophilia* sepsis in 12 subjects, due to the use of reprocessed high-flux membranes with contaminated O-rings inside the dialyser; 4 out of 12 patients and 21 patients as described by Flaherty *et al.* (1993) and Roberts *et al.* (1994), respectively.

Manual or automated peritoneal dialysis is performed by introducing a dialysis solution into the abdominal cavity through a permanent tunneled catheter and most peritoneal dialysis literature on *S. maltophilia* addresses peritoneum and/or peritoneal catheter exit site infections. The

Table 1. Summary of the original articles published to date dealing with *Stenotrophomonas maltophilia* contamination or infection in patients with end stage renal disease

Topic	No. of articles	No. of patients	References
Environment contamination	3	12	Flaherty *et al.* (1993); Roberts *et al.* (1994); Arvanitidou *et al.* (2003)
Peritoneal dialysis	9	28	Berbari *et al.* (1993); Szeto *et al.* (1997); Taylor *et al.* (1999); Al-Hilali *et al.* (2000); Cheng *et al.* (2001); Baek *et al.* (2004); Machuca *et al.* (2005); Lee *et al.* (2009); Tzanetou *et al.* (2004)
Haemodialysis	4	5	Ganadu *et al.* (1996); Korzets *et al.* (1997); Kara *et al.* (2006); Shah & Feinfeld (2000)
Other	1	18	Wakino *et al.* (2009)

earliest reports recommended a prolonged antibiotic treatment and the removal of catheters (Berbari *et al.*, 1993; Szeto *et al.*, 1997; Taylor *et al.*, 1999; Alhilali *et al.*, 2000), perhaps due to the severity of the infection and also as is usual clinical practice. In more recent years, a tunneled catheter was removed in a woman with exit site infection due to *S. maltophilia* with multi-resistant antibacterial spectrum, a condition at high risk of peritonitis (Cheng *et al.*, 2001). Nevertheless, as described by Taylor *et al.* (1999), three out of seven catheters were saved after a prolonged systemic therapy. More recently, a longer therapy with trimethoprim/sulfamethoxazole in combination with one or two additional agents (quinolones or aminoglycosides) has proved useful in preventing the removal of catheters (Baek *et al.*, 2004; Tzanetou *et al.*, 2004). In one study, four out of five catheters were maintained by treating peritonitis with a combination therapy of intraperitoneal ceftazidime plus endovenous trimethoprim and/or amikacin for a period of two weeks to two months (Baek *et al.*, 2004). Another study reports the treatment of a *S. maltophilia* peritoneal infection through intraperitoneal instillation of ceftazidime and endovenous trimethoprim plus ticarcillin or amikacin for two to four weeks, saving three out of four catheters; the fourth catheter was removed because of fungal co-infection (Tzanetou *et al.*, 2004). An additional study reports the successful treatment of *S. maltophilia* peritonitis in a female patient undergoing automated peritoneal dialysis with trimethoprim/sulfamethoxazole for 6 weeks and amikacin for 2 weeks (Machuca *et al.*, 2005). Recently, a strategy to treat refractory *S. maltophilia*-related peritonitis has been proposed: the association of an antibiotic lock therapy, for example with a third-generation cephalosporin, after each peritoneal exchange in addition to the local instillation of antibiotics inside the peritoneum (Lee *et al.*, 2009).

Few papers deal with *S. maltophilia*-related bacteraemia in dialysis patients with permanent central venous catheters. One paper reports treating a tunneled central venous catheter infection (due to *S. maltophilia*) with endovenous ciprofloxacin and the removal of the catheter (Ganadu *et al.*, 1996). Another paper reports that the use of trimethoprim/sulfamethoxazole alone resolved the infection in two patients who experienced pancytopenia during therapy; however, in both cases catheters were removed (Korzets *et al.*, 1997). In addition, one group reported successfully treating infected patients with a combination of trimethoprim/sulfamethoxazole and ciprofloxacin, and

Table 2. *Stenotrophomonas maltophilia*-related catheter infections with regard to catheter outcome

Catheters	Total no. of patients (gender, age)	No. of catheters replaced	No. of catheters not replaced	Reference
Peritoneal dialysis catheters	1 (NA)	1	–	Berbari *et al.* (1993)
	6 (NA)	6	–	Szeto *et al.* (1997)
	7 (3M, 16–61y)	4	3	Taylor *et al.* (1999)
	2 (NA)	2	–	Al-hilali *et al.* (2000)
	1 (M, 47y)	1	–	Cheng *et al.* (2001)
	5 (2M, 34–62y)	1	4	Baek *et al.* (2004)
	1 (F, 54y)	–	1	Machuca *et al.* (2005)
	1 (NA)	–	1	Lee *et al.* (2009)
	4 (2M, 40–64y)	1	3	Tzanetou *et al.* (2004)
Haemodialysis catheters	1 (M, 72y)	1	–	Ganadu *et al.* (1996)
	2 (F, 39y; M, 63y)	2	–	Korzets *et al.* (1997)
	1 (F, 43y)	1	–	Kara *et al.* (2006)
	1 (F, 37y)	–	1	Shah & Feinfeld (2000)

M, Male; F, female; y, years; NA, not available.

removal of the catheter (Kara *et al.*, 2006). Finally, a case of a *S. maltophilia* infection in a dialysed woman with a tunneled central venous catheter has been described by Shah & Feinfeld (2000): since a combination therapy of ceftazidime and ciprofloxacin failed to eradicate the infection, the addition of a long-term daily locked-in therapy with ceftazidime was able to save both the catheter and the patient.

To our knowledge there is only one study analysing *S. maltophilia* infections, not related to the dialysis vascular access, among uraemic subjects. As described by Wakino *et al.* (2009), 18 out of 199 (9 %) bacteria from 120 dialysed patients, diagnosed with nosocomial pneumonia, were *S. maltophilia*. The pathogen was resistant to carbapenems, cephalosporins and ciprofloxacin, but sensitive to newer-generation quinolones. Two-thirds of patients died, confirming the higher mortality among the dialytic population.

Discussion

Among dialysed subjects, *S. maltophilia*-related infections could be challenging and life-threatening because of antibiotic resistance of the bacterium and the immunosuppresed status of uraemic patients. In addition, it must always be considered that *S. maltophilia* may not be the only pathogen involved in the infection, as *S. maltophilia* is frequently accompanied by Gram-positive bacteria, mainly *Enterococcus faecalis* (Wakino *et al.*, 2009).

Finally we would like to use the available literature to give some suggestions in order to optimize the antibiotic therapy and preserve, whenever possible, the patient and the catheter.

1) When the infection is not accompanied by severe clinical symptoms or when the substitution of the catheter is not easily achievable (for instance, patients with multiple access failures and with previous central venous catheterizations or thrombosis): provide a long-course (2–4 weeks) intravenous administration of, at least, two antibiotics combined with the locked-in therapy. The catheter may remain *in situ*.

2) If the infection is mildly symptomatic a long course of antibiotic therapy, as in point one, can be pursued but if fever does not disappear in 48–72 h, replace the central venous catheter and continue systemic and local antibacterial therapy.

3) When the infection is accompanied by severe clinical symptoms or relapses in a few months: provide a long-course (2–4 weeks) intravenous infusion of, at least, two antibiotics combined with the locked-in therapy. If a co-infection is evident, add an adequate therapy. Remove the infected catheter and replace with a new catheter in a different vein or abdominal area, for haemo- or peritoneal dialysis, respectively.

According to the susceptibility of the bacterium, a prolonged combination therapy of endovenous aminoglycosides plus levofloxacin or ceftazidime or trimethoprim/sulfamethoxazole, and a locked-in instillation of gentamicin or ceftazidime, is safe, with an excellent outcome for both the patient and the catheter.

Conclusion

S. maltophilia is an emergent pathogen in dialysis units, causing infection in peritoneal and haemodialysis patients; since it is also a natural inhabitant in most environments inside and outside the hospital setting, it can induce infections in immunosuppressed subjects. The treatment of *S. maltophilia*-related infection could be cumbersome because of several bacterial and host characteristics. Antibiotic therapy, if well conducted, is able to cure the infection in most cases; in a few, it preserves patient safety and dialysis access patency.

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