BURKHOLDERIA CEPACIA EXIT-SITE INFECTION IN PERITONEAL DIALYSIS PATIENTS—CLINICAL CHARACTERISTICS AND TREATMENT OUTCOMES

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◆ **Background:** *Burkholderia cepacia* is a hardy bacterium with intrinsic resistance to multiple antibiotics and high transmissibility. Opportunistic healthcare-associated *B. cepacia* infections among immunocompromised or critically ill patients have been reported, but there is limited data on the clinical characteristics and treatment outcomes of exit-site infection (ESI) in peritoneal dialysis (PD) patients.

◆ **Patients and methods:** Patients who suffered from *B. cepacia* ESI from 1 January 2004 to 31 December 2014 were reviewed. The clinical characteristics and treatment outcomes of the patients and the antibiotic susceptibility patterns of the bacterial isolates were analyzed.

◆ **Results:** Twenty-two patients were included for analysis. Eight patients (36.4%) had medical conditions which impaired host immunity, while 7 (31.8%) had pre-existing skin abnormalities. Three patients (13.6%) progressed to tunnel-tract infection and another 3 patients (13.6%) developed associated peritonitis. Fifteen patients (68.2%) responded to medical treatment while 7 (31.8%) required catheter removal. Eleven patients (50.0%) had recurrent *B. cepacia* ESI, which occurred at 7.8 months (95% confidence interval [CI] 0.1 – 19.4 months) after the first episode. Most *B. cepacia* strains were susceptible to ceftazidime (95.5%), piperacillin/tazobactam (95.5%), and piperacillin (90.9%). Besides aminoglycosides (80 – 100%), high rates of resistance were also observed for ticarcillin/clavulanate (90.9%).

◆ **Conclusion:** *Burkholderia cepacia* ESI is associated with low rates of tunnel-tract infection or peritonitis, but the risk of recurrence is high. Most cases can be managed with medical treatment alone, although one third of patients might require catheter removal.

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Exit-site infection (ESI) is a common and important clinical problem in patients on peritoneal dialysis (PD) and is associated with increased risk of catheter loss, peritonitis,

and subsequent peritoneal failure (1–3). In addition to common causative organisms of ESI including *Staphylococcus aureus*, coagulase-negative *Staphylococcus*, and *Pseudomonas aeruginosa* (1–4), multi-drug resistant opportunistic pathogens have emerged as causative agents of ESI in PD patients. One illustrative example is *Burkholderia cepacia*, which is a ubiquitous organism commonly found in plant roots, soil, and moist environments (5,6). *Burkholderia cepacia* infection usually affects cystic fibrosis patients and immunocompromised hosts (5–8). Nosocomial outbreaks have occurred in intensive care and dialysis units due to contaminated medical devices and dialysis solutions (8–11), but *B. cepacia* ESI in PD patients has rarely been reported (12). The ubiquity, intrinsic resistance to multiple antibiotics, and high transmissibility of *B. cepacia* contribute to the bacterium's ability to cause ESI in PD patients. However, there is currently scarce data on the clinical features and treatment outcomes of *B. cepacia* ESI. This retrospective study aimed to review the clinical characteristics, antibiotic susceptibility patterns, and treatment outcomes of PD patients with *B. cepacia* ESI.

PATIENTS AND METHODS

All case records of end-stage renal failure patients who received long-term PD and were followed up at Queen Mary Hospital or Tung Wah Hospital, Hong Kong, from 1 January 2004 to 31 December 2014 were reviewed. Patients who had suffered from *B. cepacia* ESI were included for analysis. All patients attended the day centers and renal wards of their respective dialysis units. *Burkholderia cepacia* ESI was defined by a positive microbiological culture of *B. cepacia* in the purulent discharge from the exit site, with or without erythema of the skin at the catheter-epidermal interface (1). Tunnel-tract infection was recognized as erythema, edema, or tenderness along the tunnel tract of the PD catheter (1). *Burkholderia cepacia*-associated peritonitis was denoted by: 1) total PD fluid cell count > 100/cm³ (> 50% polymorphonuclear neutrophils); 2) presence of abdominal pain or fever; 3) a positive microbiological culture of *B. cepacia* in the PD fluid (1). All patients with *B. cepacia* ESI received topical treatment with 0.05% chlorhexidine gluconate or 5.85% NaCl. Systemic antibiotics

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were initiated at the clinicians' discretion and modified when the antibiotic susceptibility results were available. The standard duration of antibiotic treatment in our center was 14 days. Patients with *B. cepacia* peritonitis were treated with intraperitoneal antibiotics according to the antibiotic susceptibility results. The PD catheter was removed when peritonitis failed to respond to appropriate intraperitoneal antibiotics treatment after 5 consecutive days. Antibiotic susceptibility tests were performed using the Kirby-Bauer disk diffusion method and interpreted according to the Clinical and Laboratory Standards Institute criteria. "Resolution of ESI" was denoted by the disappearance of purulent discharge and erythema at the exit site. "Recurrence" was defined as reappearance of ESI due to the same organism 4 weeks after resolution of ESI. "Refractory ESI" referred to cases which did not improve after 14 days of appropriate antibiotic treatment. In our center, healthcare professionals were required to use alcohol hand-rub and wear gloves before handling exit sites. The clinical characteristics, medical comorbidities, complications including tunnel-tract infection and peritonitis, antibiotic susceptibility patterns, treatment modalities, and outcomes of these patients were analyzed. Continuous variables are expressed as mean $\pm$ standard deviation (SD) or median (range) where appropriate. Categorical variables were expressed as frequencies and percentages (95% confidence interval [CI]). The mean recurrence-free survival time was estimated using Kaplan Meier methods.

RESULTS

PATIENT DEMOGRAPHICS AND RISK FACTORS

During the study period with a total follow-up of 2,141 patient-months (median duration 73.8 months; range 11.0 – 252.1 months), 22 patients with *B. cepacia* ESI were included for analysis. The patient demographics are summarized in Table 1. Eleven cases (50%, 95% CI 29.2 – 71.0%) occurred from 1 January 2013 to 31 December 2014, 8 patients (36.4%, 95% CI 16.3 – 56.5%) had medical conditions which were associated with impaired host immunity while 7 (31.8%, 95% CI 12.4– 51.3%) had pre-existing skin diseases or exit-site abnormalities. Seven patients (31.8%, 95% CI 12.4 – 51.3%) had other concomitant organisms isolated from the exit site (Table 1). All patients came from an urban area, and we observed no seasonal variation in *B. cepacia* peritonitis (spring (March – May): 4 episodes; summer (June – August): 6 episodes; autumn (September – November): 5 episodes; winter (December – February): 7 episodes).

ASSOCIATION WITH TUNNEL-TRACT INFECTION AND PERITONITIS

Three patients (13.6%, 95% CI 3.0 – 35.0%) progressed to tunnel-tract infection (1 had systemic lupus erythematosus, 1 had failed kidney allograft, and 1 showed resistance to ceftazidime), and all failed medical treatment and required catheter removal. Three patients (13.6%, 95% CI 3.0 – 35.0%)

TABLE 1
Clinical Characteristics of 22 Peritoneal Dialysis Patients Who Suffered from *Burkholderia Cepacia* Exit-Site Infection

Patient demographics	
Age (years)	61.9 $\pm$ 12.0
Sex (M/F)	11/11
Duration of dialysis (months)	53.1 $\pm$ 63.7
Causes of renal failure	
Unknown cause	10 (45.5%)
Diabetic nephropathy	6 (27.3%)
Obstructive uropathy	3 (13.6%)
Lupus nephritis	1 (4.5%)
IgA nephropathy	1 (4.5%)
Polycystic kidney disease	1 (4.5%)
Other medical comorbidities	
Hypertension	8 (36.4%)
Ischemic heart disease	4 (18.2%)
Stroke	1 (4.5%)
Systemic lupus erythematosus	1 (4.5%)
Chronic hepatitis B infection	1 (4.5%)
Failed kidney allograft	1 (4.5%)
Clinical characteristics	
Use of antibiotics in the preceding 4 weeks	4 (18.2%)
Pre-existing skin disease/exit-site abnormalities	7 (31.8%)
Existing granuloma	4 (18.2%)
Protruding external cuff	2 (9.1%)
Chronic eczema	1 (4.5%)
Concomitant organisms identified in the exit site	
Coagulase negative <i>Staphylococcus</i> (CNS)	3 (13.6%)
<i>Pseudomonas aeruginosa</i>	2 (9.1%)
Methicillin-sensitive <i>Staphylococcus aureus</i> (MSSA)	1 (4.5%)
<i>Acinetobacter baumannii</i>	1 (4.5%)
Associated tunnel-tract infection	3 (13.6%)
Associated peritonitis	3 (13.6%)

developed *B. cepacia* peritonitis (2 had diabetes mellitus; the remaining 1 was the patient with concomitant tunnel-tract infection with ceftazidime-resistant strain); none of them responded to intraperitoneal antibiotic treatment and all required catheter removal. Two of them could resume PD after peritonitis resolved, but 1 required switching to permanent hemodialysis.

TREATMENT MODALITIES AND OUTCOMES

Seventeen patients (77.3%, 95% CI 59.8 – 94.8%) received systemic antibiotics. Five patients were treated with oral antibiotics alone (levofloxacin $n = 3$; amoxicillin/clavulanic acid $n = 1$; cephalexin $n = 1$), and all showed resolution of ESI. Twelve patients (54.5%, 95% CI 33.7 – 75.4%) received oral, followed by intravenous, antibiotics (ceftazidime $n = 9$; piperacillin/tazobactam $n = 2$; ticarcillin/clavulanic acid $n = 1$), and 5 of them showed favorable response to intravenous antibiotics. Five patients only received topical treatment (0.05% chlorhexidine gluconate $n = 4$; 5.85% NaCl dressing

$n = 1$), and all showed resolution of ESI. Taken together, a total of 15 patients (68.2%, 95% CI 48.7 – 87.6%) responded to medical treatment. Seven patients (31.8%, 95% CI 12.4 – 51.3%) required PD catheter removal due to tunnel-tract infection ($n = 2$), peritonitis ($n = 2$), refractory ESI ($n = 2$), and concomitant tunnel-tract involvement and peritonitis which were resistant to ceftazidime ($n = 1$). Risk factors identified among these 7 patients who required catheter removal included diabetes mellitus ($n = 2$), systemic lupus erythematosus ($n = 1$), failed kidney allograft ($n = 1$), and ceftazidime-resistant strain ($n = 1$). Eleven patients (50%, 95% CI 29.1 – 71.0%) had recurrent *B. cepacia* ESI (Table 2). The mean recurrence-free survival was 7.8 months (95% CI 0.1 – 19.4 months). Among these eleven patients, 7 (63.6%, 95% CI 35.2 – 92.1%) were treated previously with either topical treatment or oral antibiotics alone while the remaining 4 patients previously had refractory *B. cepacia* infection which required catheter removal.

ANTIBIOTIC SUSCEPTIBILITY PATTERNS

The antibiotic susceptibility patterns are summarized in Table 3. Most *B. cepacia* strains were sensitive to ceftazidime (95.5%), piperacillin/tazobactam (95.5%), piperacillin (90.9%), and 81.8% of cases were sensitive to cotrimoxazole. As expected, most strains were resistant to aminoglycosides (gentamicin – 100%; amikacin – 81.2%; tobramycin 81.9%). Most strains were resistant to ticarcillin/clavulanic acid (90.9%).

DISCUSSION

Our study was the first series to report the clinical characteristics and treatment outcomes of *B. cepacia* ESI in PD patients. In this cohort, more than one third of our patients had medical conditions which contributed to impaired host immunity, and this was in line with previous studies that *B. cepacia* infection in non-cystic fibrosis patients usually occurred in immunocompromised hosts (5,7). Although nosocomial outbreaks of *B. cepacia* infection have been previously reported in intensive care and dialysis units (8–11), there was no clustering among cases in our cohort to suggest nosocomial outbreaks. Pre-existing skin diseases or exit-site abnormalities such as granuloma or protruding external Tenckhoff cuffs, which occurred in up to 30% of our patients, might also be other predisposing factors for *B. cepacia* ESI.

In this study, we found that *B. cepacia* ESI was associated with a relatively low rate (13.8%) of tunnel-tract infection or peritonitis. However, once tunnel-tract infection or peritonitis occurred, catheter loss was almost inevitable. Patients at risk of progression to tunnel-tract infection or peritonitis were those with impaired host immunity (diabetes mellitus, systemic lupus erythematosus, and failed kidney graft) and those with ceftazidime-resistant *B. cepacia*. Up to 70% of patients responded favorably to medical treatment with either

TABLE 2
Initial Management and Treatment Outcomes of 22
Peritoneal Dialysis Patients Who Suffered from
Burkholderia Cepacia Exit-Site Infection

Initial treatment and outcomes	
Initial treatment	
Topical treatment alone	5 (22.7%)
Systemic antibiotics	17 (77.3%)
Oral antibiotics alone	5 (22.7%)
Oral followed by intravenous antibiotics	12 (54.5%)
Treatment outcomes	
Resolved with medical treatment	15 (68.2%)
Catheter removal	7 (31.8%)
Recurrent <i>B. cepacia</i> ESI	11 (50.0%)

B. cepacia ESI = *Burkholderia cepacia* exit-site infection.

TABLE 3
Antibiotics Sensitivity/Resistance Patterns of 22
Peritoneal Dialysis Patients Who Suffered from
Burkholderia Cepacia Exit-Site Infection

	Sensitive	Moderately resistant	Resistant
Amikacin	13.6%	4.5%	81.9%
Ceftazidime	95.5%	—	4.5%
Ciprofloxacin	68.2%	27.3%	4.5%
Cefeprozoxone/sulbactam	50.0%	13.6%	36.4%
Gentamicin	—	—	100%
Imipenem	59.1%	9.1%	31.8%
Meropenem	77.3%	9.1%	13.6%
Minocycline	72.7%	9.1%	18.2%
Piperacillin	90.9%	—	9.1%
Cotrimoxazole	81.8%	13.6%	4.6%
Ticarcillin/clavulanic acid	9.1%	—	90.9%
Tobramycin	13.6%	4.5%	81.9%
Piperacillin/tazobactam	95.5%	—	4.5%

topical dressings or systemic antibiotics. However, up to 30% of patients still required PD catheter removal, and such a catheter removal rate was higher than that of *Pseudomonas aeruginosa* (17% – 27%)—another non-glucose-fermenting gram-negative bacillus notorious for refractory ESI (4,13,14). In this context, patients with impaired host defense, ceftazidime-resistant *B. cepacia* strains, and progression to tunnel-tract involvement or peritonitis appeared to be at increased risk for catheter loss. Recurrence was also common, which occurred in half of our patients at approximately 5 months after the first episode. In this study, possible risk factors for recurrence include prior treatment with topical dressing or oral antibiotics alone and previous refractory *B. cepacia* ESI which required catheter removal. Furthermore, it remained possible that the formation of biofilm on PD catheters also rendered *B. cepacia* difficult to eradicate, hence the high recurrence

rates (15,16). Another possible reason might be the relatively short duration of treatment in our patients, as *B. cepacia* was quite similar to *Pseudomonas* which required antibiotics up to 3 weeks (1).

In this series, *B. cepacia* appeared to be mostly sensitive to ceftazidime (95%) and piperacillin/tazobactam (90%). Previous studies have reported that the sensitivity of *B. cepacia* to ceftazidime and piperacillin/tazobactam varies from 23.0 – 97.3% and 15.6 – 97.3%, respectively (7,8,16–20). Our results suggested that intravenous ceftazidime or piperacillin/tazobactam were appropriate treatment of *B. cepacia* ESI. Some previous studies have also suggested the use of cotrimoxazole for the treatment of *B. cepacia* infection in non-dialysis populations (7,16,18). Our data demonstrated that the sensitivity of *B. cepacia* to cotrimoxazole was up to 80%, which was in line with previous reports and hence could also be considered a viable oral alternative (7,16,18). However, whether the significant dose reduction of cotrimoxazole in dialysis patients might compromise its efficacy remained a concern for its use in *B. cepacia* ESI. As expected, high resistance rates to aminoglycosides was observed, likely due to the presence of aminoglycoside-modifying enzymes and resistance-nodulation-division family efflux transporters (21,22). Of note, most strains were also found resistant to ticarcillin/clavulanate. Our data suggested that aminoglycosides and ticarcillin/clavulanate were not suitable treatment for *B. cepacia* ESI. Furthermore, commonly used exit-site prophylaxis such as gentamicin ointment might also select out aminoglycoside-resistant organisms such as *B. cepacia* to cause ESI in PD patients. Chlorhexidine solution, a commonly used wound dressing agent, was previously associated with *B. cepacia* contamination and increased risk of sclerosing peritonitis (10,23,24). Although our chlorhexidine solution had not been tested for *B. cepacia*, patients in this study did not use the same batch of chlorhexidine and hence this possible source of contamination was less likely. In this context, 0.9% NaCl, 20% NaCl or polyhexanide can also be used as viable alternative wound dressing agents (25). Limitations of this study include the fact that patients who were diagnosed in recent years might have lower recurrence time risk than other patients, which could result in an underestimation of the risk of recurrence. Due to the retrospective nature and small number of patients, it would also be difficult to assess the impact of humidity, seasonality, and rural or urban environment on *B. cepacia* ESI. Case-control or multi-center studies might help to generate bigger sample size and improve the level of scientific evidence on this clinical entity.

CONCLUSION

Burkholderia cepacia ESI is associated with low rates of tunnel-tract infection and peritonitis, but has high rates of recurrence. Most cases can be managed successfully with medical treatment consisting of susceptible antibiotics, although one third of patients eventually required catheter removal.

DISCLOSURES

The authors have no financial conflicts of interest to declare.

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