IVYSPRING INTERNATIONAL PUBLISHER

International Journal of Medical Sciences

2013; 10(9):1092-1098. doi: 10.7150/ijms.6251

Research Paper

Citrobacter Peritoneal Dialysis Peritonitis: Rare Occurrence with Poor Outcomes

Chia-Ter Chao[1,2], Szu-Ying Lee[3], Wei-Shun Yang[4], Huei-Wen Chen[2], Cheng-Chung Fang[2,5], Chung-Jen Yen[2,6], Chih-Kang Chiang[2,7], Kuan-Yu Hung[2], Jenq-Wen Huang[2]✉

1. Department of Traumatology, National Taiwan University Hospital, Taipei, Taiwan;
2. Division of Nephrology, Department of Internal Medicine; National Taiwan University Hospital, Taipei, Taiwan;
3. Division of Nephrology, Department of Internal Medicine, National Taiwan University Hospital Yun-Lin Branch, Yun-Lin County, Taiwan;
4. Division of Nephrology, Department of Internal Medicine, National Taiwan University Hospital Hsin-Chu Branch, Hsin-Chu County, Taiwan;
5. Department of Emergency Medicine, National Taiwan University Hospital, Taipei, Taiwan;
6. Department of Geriatrics and Gerontology, National Taiwan University Hospital, Taipei, Taiwan;
7. Department of Integrative diagnostics and Therapeutics, National Taiwan University Hospital, Taipei, Taiwan.

✉ Corresponding author: Jenq-Wen Huang, MD, PhD, Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei 100, Taiwan; Telephone: +886 2 23123456 ext. 63288; Fax: +886 2 23949269; email: 007378@ntuh.gov.tw.

© Ivyspring International Publisher. This is an open-access article distributed under the terms of the Creative Commons License (http://creativecommons.org/licenses/by-nc-nd/3.0/). Reproduction is permitted for personal, noncommercial use, provided that the article is in whole, unmodified, and properly cited.

Received: 2013.03.15; Accepted: 2013.06.18; Published: 2013.07.04

Abstract

Introduction: Non-*Pseudomonas* gram-negative bacteria are responsible for an increasing proportion of cases of peritoneal dialysis (PD)-related peritonitis. The role of *Citrobacter* species in the etiology of PD-related peritonitis is often underestimated. In the present study, we aimed to describe the clinical features, laboratory findings, and short- and long-term outcomes in PD-related peritonitis caused by *Citrobacter*.

Methods: A retrospective review of all episodes of PD-related peritonitis caused by *Citrobacter* from a single center between 1990 and 2010 was performed. Clinical features, microbiological data, and outcomes of these episodes were analyzed.

Results: *Citrobacter* species was responsible for 11 PD-related episodes (1.8% of all peritonitis episodes) in 8 patients. *Citrobacter freundii* was the most common etiologic species (73%), and mixed growth was found in the other 3 episodes (27%). Approximately half (46%) of the episodes were associated with constipation and/or diarrhea. Of the *Citrobacter* isolates from all episodes, 54% were resistant to cefazolin, and only 18% were susceptible to cefmetazole. All isolates were susceptible to ceftazidime, cefepime, carbapenem, and aminoglycosides. More than half of the patients (54%) were hospitalized for index peritonitis, and 27% of the episodes involved a change in antibiotic medication. One patient had relapsing peritonitis caused by *C. koseri* (9%). The mortality rate of PD-related peritonitis caused by *Citrobacter* was 18%, and 89% of surviving patients developed technique failure requiring a modality switch after an average of 12 months of follow-up (range 1.2–31.2 months).

Conclusion: PD-related peritonitis caused by *Citrobacter* is associated with poor outcomes, including high rates of antibiotic resistance, a high mortality rate, and a high rate of technique failure among survivors during the follow-up period.

Key words: *Citrobacter*; end-stage renal disease; gram-negative bacteria; peritoneal dialysis; peritonitis.

Introduction

Peritonitis is the major infectious complication observed in patients undergoing peritoneal dialysis (PD), accounting for nearly one-fourth of hospitalizations and cases of technique failure and catheter loss [1-3]. Gram-negative bacteria (GNB) are responsible for 15–30% of peritonitis cases. This percentage is

gradually increasing, as the number of cases caused by gram-positive bacteria continues to decline, due to the improvement in exchange systems and the use of topical anti-staphylococcal medications [4-7]. Peritonitis episodes caused by GNB are more often associated with adverse outcomes than those caused by gram-positive bacteria [8, 9].

GNB consist primarily of members of Enterobacteriaceae and other non-fermentative GNB [4, 10]. By virtue of their ability to form biofilms, these GNB are potentially less susceptible to antibiotics effective *in vivo* [11]. Recently, the term, "SPICE," has been proposed as an acronym for a group of several GNB—including *Serratia*, *Pseudomonas*, Indol-positive organisms (such as *Proteus* and *Acinetobacter*), *Citrobacter*, and *Enterobacter*—recognized for their increased potential to induce treatment failure and cause relapsing peritonitis [12, 13]. These pathogens possess inducible chromosomally mediated beta-lactamase, which increases their probability of developing *in vivo* resistance to administered penicillin or cephalosporins [14]. Consequently, physicians should be alert to the potential presence of these organisms when prescribing appropriate antibiotics for PD-related peritonitis.

Among the SPICE pathogens, *Citrobacter* species have a low incidence of pathogenicity. Data from the ANZDATA registry show that *Citrobacter* species are responsible for only 1.7% of all non-*Pseudomonas* PD-related peritonitis episodes, which is significantly fewer than those caused by *Enterobacter* (8.8%), *Serratia* (8.2%), and other Indol-positive GNB (8.1%) [7]. Szeto and colleagues also reported that *Citrobacter* species account for only 4.8% of all Enterobacteriaceae peritonitis cases, which is fewer than those caused by *Enterobacter* (5.8%) and *Serratia* (8.6%) [9]. Previous articles describing PD-related peritonitis caused by *Citrobacter* have all been case reports, and have been limited both in patient number (fewer than 3) and in available laboratory and clinical data, such as antibiograms [15-18]. In the present study, we aimed to report our experience with PD-related peritonitis caused by *Citrobacter*, and also describe the clinical features and course, microbiological data, and short- and long-term outcomes of these cases.

Materials and Methods

Ethical considerations

The ethics committee of the NTUH approved the current study (NO. 201212165RINC). The local institutional review board did not mandate patient consent, since no interventions were made and patient privacy was not breached.

Study design, setting, and clinical data collection

This was a retrospective analysis of a prospectively assembled cohort of the National Taiwan University Hospital (NTUH) PD program [19]. Only conventional Tenckhoff catheters (double-cuffed and straight) were utilized in our institute, with exit site orientated downward. Also, all the PD catheters were inserted by surgeons with laparoscopic approach, without ultrasound guidance. In our PD registry, all patients with end-stage renal disease (ESRD) initiated on PD or initially on hemodialysis but later switched to PD in our institute were identified and entered into our PD registry. Only patients under maintenance PD for more than 3 months were eligible in the current study. We identified all patients with episodes of culture-confirmed *Citrobacter* species-associated peritonitis between 1990 and 2010. Peritonitis was diagnosed according to the presence of symptomatology and cloudy effluent with leukocyte count >100/μL since 1985, but the diagnostic criteria were later expanded to include neutrophils >50% of effluent leukocytes to better accommodate international guidelines after 1990 [20].

We reviewed all PD patients' demographic profiles, which included age and gender; their comorbidities, such as diabetes mellitus (DM), congestive heart failure (CHF), liver cirrhosis, and history of autoimmune diseases; and the causes of their primary renal disease. The patients' regular medications, including steroids and immunosuppressants, were recorded. Antibiotics use within 1 month of the peritonitis episode was also recorded.

For each episode of PD-related peritonitis caused by *Citrobacter*, we documented the PD vintage and modality (continuous ambulatory peritoneal dialysis [CAPD] or automated peritoneal dialysis [APD]); the patient's initial symptoms; pathogens identified; and antibiograms. In addition, laboratory data were obtained. The presumed etiology of peritonitis included break in sterility during the exchange procedure, constipation and/or diarrhea associated (potentially gastrointestinal [GI] flora transmural migration) [21-23], major intra-abdominal events (diverticulitis or perforated viscus), and undetermined. Recommendations for empirical antibiotic regimen for PD peritonitis varied with time. Vancomycin/aminoglycoside were initially favored in 1980s for better coverage of resistant pathogens, but subsequently replaced by first-generation cephalosporin/aminoglycoside or third-generation cephalosporin during late 1990s for fear of vancomycin-resistance emergence and adverse effects of aminoglycoside on residual renal function [20, 24]. In our PD program, empirical antibiotics for patients with peritonitis included intraperitoneal

cefazolin/aminoglycoside (before 1998) or cefazolin/ceftazidime (after 1998), according to International Society for Peritoneal Dialysis (ISPD) recommendations, unless otherwise indicated [12, 25, 26].

Outcome variables

The outcome measures examined included short- and long-term components. Short-term outcomes of index peritonitis consisted of primary response, antibiotic switch (secondary response), relapse peritonitis, repeat peritonitis, Tenckhoff catheter removal, temporary or permanent transfer to hemodialysis, and patient death. The primary response was defined as symptomatic improvement of the patient with effluent leukocyte count <100/μL within 3 days of receiving first-line antibiotic treatment. The secondary response was defined as a response to the second-line antibiotic treatment when a clear effluent was not noted following treatment with first-line antibiotics [12, 25, 26]. Repeat peritonitis was defined as peritonitis recurring after 4 weeks of the previous episode involving the same pathogen, whereas relapse peritonitis was defined as peritonitis recurring within 4 weeks after treatment of the previous episode involving the same pathogen [12, 25, 26]. Peritonitis-related death was considered if the patient's death occurred within 1 month of the peritonitis episode and was attributable to peritonitis.

In addition, we followed each patient until end of 2012. Long-term outcomes of index peritonitis included technique failure, with a modality switch to hemodialysis.

Results

Clinical features of PD-related peritonitis caused by Citrobacter

During the study period, a total of 328 patients developed PD-related peritonitis over 35,211 patient-months, with an overall peritonitis incidence of 1 per 56 patient-months. Among the 627 episodes of PD-related peritonitis, 8 patients developed 11 episodes caused by *Citrobacter* species (1.8% of all episodes). One patient developed 3 separate episodes within 3 years, another developed 2 episodes within 3 years, and the remaining patients each developed 1 episode. All *Citrobacter* PD peritonitis episodes occurred when the patients were using dianeal 1.5% or 2.5% dialysate.

The demographic profiles and clinical characteristics of patients developing PD-related peritonitis caused by *Citrobacter* and other members of Enterobacteriaceae are listed in Table 1. The mean age of patients with *Citrobacter* peritonitis was 53 years, significantly younger than ones with peritonitis from other Enterobacteriaceae; 63% of the patients were male. The mean PD duration of patients with *Citrobacter* peritonitis was 36 months (range, 3–71). Most *Citrobacter* peritonitis patients had no comorbidities, except for CHF (25%). The most common etiology that resulted in the requirement for dialysis in *Citrobacter* peritonitis patients included chronic glomerulonephritis (75%), followed by DM (13%) and hypertension (13%).

Table 1. Baseline features of patients with *Citrobacter* PD-associated peritonitis.

Characteristics	*Citrobacter* (n=8)	non-*Citrobacter* Enterobacteriaceae members (n=161)	*P* value
Age (years)	53 (25 – 74)	60 (22 – 89)	0.021
Men (%)	5 (63)	61 (38)	0.259
Modality (CAPD)(%)	4 (50)	100 (62)	0.978
Vintage (months)	36 (3 – 71)	37 (3 – 127)	0.765
Comorbidities			
DM	1 (13)	39 (24)	0.351
CHF	2 (25)	14 (9)	0.115
Liver cirrhosis	1 (13)	10 (6)	0.452
Cause of primary renal diseases			0.102
DM	1 (13)	31 (19)	
CGN	6 (75)	74 (46)	
Hypertension	1 (13)	31 (19)	
PCKD	0 (0)	8 (5)	
Unknown	0 (0)	917(11)	
Laboratory data			
Hemoglobin (g/dL)	10.0 (5.7 - 13.1)	10.0 (6.2 – 14.9)	0.074
Albumin (mg/dL)	3.9 (3.2 - 4.6)	3.8 (2.6 – 4.9)	0.696
Creatinine (mg/dL)	10.7 (5.0 - 13.7)	10.0 (4.6 – 17.9)	0.582
Total cholesterol (mg/dL)	233 (161 - 299)	200.3 (90 – 329)	0.518

Continuous variables are expressed in mean (ranges), while categorical variables are expressed in number (percentage). Abbreviations: APD, ambulatory peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; CGN, chronic glomerulonephritis; CHF, congestive heart failure; DM, diabetes mellitus; PCKD, polycystic kidney disease.

None of the patients had undergone intra-abdominal surgery or endoscopy before the development of index peritonitis. In addition, none of the patients had taken antibiotics in the month prior to developing index peritonitis, and none of the patients had been prescribed any steroid or immunosuppressant medications. The presenting symptoms of PD-related peritonitis caused by *Citrobacter* were abdominal pain (100%), followed by fever (27%), nausea/vomiting (18%), and diarrhea (9%). All patients exhibited a turbid dialysate. The mean effluent leukocyte counts were 9200/μL (range, 500–46,500/μL), with 92% neutrophils. The initial blood leukocyte levels were 9744/μL (range, 4430–17,560/μL), with 85% neutrophils. The most common species from the effluent was *Citrobacter freundii* (73%), followed by *C. koseri* (27%); the cultures

from 3 episodes (27%) showed polymicrobial growth (all included *C. freundii*). Viridans Streptococci, *Enterobacter aerogenes*, and *Klebsiella oxytoca* were each responsible for 1 episode of polymicrobial growth. None of the patients had concomitant bacteremia or exit-site infections.

The most common cause of PD-related peritonitis caused by *Citrobacter* was constipation and/or diarrhea associated (46%), followed by break in exchange sterility (9%). Structural GI lesions were not identified in most of the patients, after upper/lower GI endoscopic examinations. No definite source could be identified in the other episodes of PD-related peritonitis caused by *Citrobacter* (46%).

The antibiotic susceptibilities of the *Citrobacter* species are shown in Table 2. Approximately 64% of *Citrobacter* species were resistant to ampicillin, followed by cefazolin (55%) and ampicillin/sulbactam (46%). The rate of resistance to cefmetazole was 27%, with another 27% showing intermediate resistance to cefmetazole. None of the *Citrobacter* isolates showed resistance to cefotaxime, ceftazidime, cefepime, carbapenem, aminoglycosides, piperacillin/tazobactam, or fluoroquinolones. With regard to the first-line antibiotic treatment, intraperitoneal cefazolin/ceftazidime was initially used in 7 episodes (64%) and intraperitoneal cefazolin/aminoglycosides was used in 3 episodes (27%; all before 1998). One patient (9%) was initially treated with intravenous vancomycin/ciprofloxacin for treatment of infection by potential nosocomial pathogens. After culture results and antibiograms available, we discontinued the antibiotic to which the pathogens were resistant or the antibiotic that was of later generation (ceftazidime) if cefazolin/ceftazidime were both effective.

A total of 6 patients (54%) required hospitalization, with a mean hospital duration of 9 days (range, 6–14 days). Table 3 lists the clinical outcomes of patients with PD-related peritonitis caused by *Citrobacter*. A primary response was achieved in 6 episodes (54%), and after switching antibiotics, a secondary response was noted in another 2 episodes (18%). The average time to antibiotic switch was 6 days (range, 3–7 days). Those responding to antibiotics were maintained on susceptible antibiotics for an average of 14 days (range, 11–21 days). Two patients (18%) with PD-related peritonitis caused by *Citrobacter* died within 2 weeks of diagnosis, both due to sepsis. One of them had no response to antibiotics at all, while the other had secondary response to antibiotics with decreasing dialysate turbidity and effluent leukocyte counts. The other patients continued PD throughout the disease period, although 1 patient (9%) later developed relapsing peritonitis. The patient with relapsing peritonitis subsequently still had primary response to cefazolin, but later developed technique failure with modality switch to hemodialysis 2.5 months later. The patients who recovered from PD-related peritonitis caused by *Citrobacter* had poor long-term outcomes. Approximately 89% of these patients had technique failure, with a subsequent change in dialysis modality within 1 year (Table 3). Five of the 8 patients had subsequent technique failure due to refractory peritonitis; the other 2 patients died due to sepsis, and the remaining patient dropped out due to ultrafiltration failure. Of the 5 patients with late refractory peritonitis related technique failure, two patients were caused by *E. coli*, one was caused by *Enterobacter aerogenes*, while the other two were caused by refractory *Citrobacter* peritonitis. The two patients died later were due to healthcare-associated pneumonia (culture negative) and intra-abdominal infection (E. coli bacteremia) respectively.

Table 2. Antibiotics susceptibility of *Citrobacter* species isolate from effluent.

Antibiotics	Susceptible (%)		Intermediate (%)		Resistant (%)		Not tested (%)	
	Citrobacter	Other Entero-bacteriaceae	*Citrobacter*	Other Enter-obacteriaceae	*Citrobacter*	Other Entero-bacteriaceae	*Citrobacter*	Other Entero-bacteriaceae
Ampicillin	0	23	9	5	64	70	27	2
Ampicil-lin/sulbactam	18	71	9	12	46	15	27	2
Piperacil-lin/tazobactam	73	96	0	1	0	0	27	3
Cefazolin	18	82	0	1	55	17	27	0
Cefmetazole	18	89	27	2	27	9	27	0
Cefotaxime	73	95	0	2	0	3	27	0
Ceftazidime	73	74	0	2	0	4	27	20
Cefepime	73	100	0	0	0	0	27	0
Imipenem	73	98	0	1	0	1	27	0
Gentamicin	73	87	0	0	0	13	27	0
Amikacin	73	85	0	0	0	0	27	15
Ciprofloxacin	73	90	0	0	0	10	27	0

Table 3. Clinical outcomes of *Citrobacter* PD-associated peritonitis episodes.

Outcomes	*Citrobacter* (n=11)	Other Enterobacteriaceae (n=161)	*P* value*
Short-term (per episode)			
Antibiotics			
Primary response (%)	6 (55)	97 (60)	0.664
Antibiotic switch (%) (Secondary response)	2 (18)	27 (17)	0.376
Time to antibiotic switch (days)	6 (3 - 7)	7 (3 – 15)	0.006
Tenckhoff catheter removal (%)	0 (0)	26 (16)	0.143
Relapse peritonitis (%)	1 (9)	0 (0)	0.005
Repeat peritonitis (%)	0 (0)	0 (0)	1.000
Mortality (%)	2 (18)	11 (7)	0.015
Time to mortality (days)	11 (7 – 14)	16 (2 – 46)	0.601
Long-term (per episode)	(n=9)	(n=150)	
Technique failure with modality switch to hemodialysis (%)	8 (89)	88 (59)	0.023
Time to technique failure (months)	13 (1 – 31)	19 (1 – 75)	0.04
Causes of Technique failure			
Refractory peritonitis (%)	5 (63)	75 (85)	
Ultrafiltration failure (%)	1 (13)	1 (1)	
Mortality (%)	2 (25)	4 (5)	
Renal transplantation (%)	0 (0)	8 (9)	

Continuous variables are expressed in mean (ranges), while categorical variables are expressed in number (percentage). * Compared with independent t-test.

Discussion

In this study of cases of PD-related peritonitis caused by *Citrobacter*, *C. freundii* was the most common *Citrobacter* species identified from the effluent, and constipation and/or diarrhea associated origin was the most common source of infection. Most *Citrobacter* isolates were resistant to first- and second-generation cephalosporins, as well as to ampicillin/sulbactam. Nearly half required hospitalization, with a high mortality rate (18%). After recovery from *Citrobacter* peritonitis, patients remained at high risk of developing technique failure within the following year.

The most common etiology of ESRD in our Citrobacter peritonitis cohort was chronic glomerulonephritis, differing from the conventional belief that DM nephropathy accounts for most ESRD (Table 1). However, ESRD patients from DM nephropathy less often received PD due to concerns of glycemic control. In addition, several PD registries reported similar findings. For example, a Hong Kong PD cohort identified glomerulonephritis to be the most common ESRD cause, followed by DM [9]. Another ANZDATA report also found glomerulonephritis to be more common than DM [7]. We suggested that both GN and DM are common etiologies than other causes, but the order of GN/DM might vary among studies.

Citrobacter species, gram-negative bacilli belonging to the Enterobacteriaceae family, are found to colonize human or animal GI tracts [27]. The main pathogenic strains are *C. koseri* and *C. freundii*, accounting for more than 70% of human infections [27-29]. In our study, *C. freundii* was the most frequent species identified from the effluent (73%). The risk factors for *Citrobacter* infections include advanced age, hospitalization, debilitation, and presence of multiple comorbidities [28, 30]. However, our PD patients had none of these risk factors but still developed *Citrobacter* peritonitis (Table 1). GI colonization by antibiotic-resistant gram-negative bacteria, such as *Citrobacter* species, might be more common in dialysis patients than the general population [31, 32]. Among these resistant gram negative bacteria, *Citrobacter* species are reportedly the most common type [33]. Furthermore, in our PD registry, we defined GI flora transmural migration as the origin of PD peritonitis, if the clinical scenarios presented with Gram-negative or polymicrobial effluent isolates in the absence of anatomically-documented bowel lesions, and in the presence of constipation and/or diarrhea. This is compatible with the constipation/diarrhea associated PD peritonitis origin in our current study. In light of these arguments and our finding, PD patients might acquire *Citrobacter* PD peritonitis more frequently through GI microbial transmural migration (45%) than PD peritonitis of other pathogens (usually 5-10%) [21,22]. We postulated that the combination of potentially higher GI colonization rate and more frequent translocation might explain the development of *Citrobacter* PD peritonitis in these patients. The potential explanations for GI microbial transmural migration include alterations of intestinal flora, mucosal

barrier dysfunction, and defective immunologic defense mechanisms [34]. In PD patients, renal failure could serve as a background of relative immunodeficiency [35], and this status underlies the susceptibility of transmural microbial migration. In addition, *Citrobacter* infections are polymicrobial in as many as 13–30% of episodes [28, 29, 36, 37], whereas in PD-related peritonitis, the overall rate of polymicrobial episodes is 10–15% on average [38]. In our study, 27% of episodes of *Citrobacter* PD peritonitis were polymicrobial, potentially contributing to the poorer outcomes [38, 39].

Citrobacter species are less susceptible to antibiotics, with high resistance to penicillin (70–90%) and cephalosporins (first generation, 40–70%; fourth generation, 1–5%), moderate resistance to aminoglycosides (10–40%), and variable resistance to quinolones [29, 36, 37, 40, 41]. Most *Citrobacter* species are susceptible to penicillin/beta-lactamase inhibitors and carbapenems (>90%) [29, 36, 37, 40]. Prior use of broad-spectrum antibiotics (especially third-generation cephalosporins), or other antibiotics (such as vancomycin), is potentially associated with resistant strains of *Citrobacter* [37, 41]. However, none of our patients had been exposed to antibiotics prior to developing current peritonitis.

Among all multidrug-resistant Enterobacteriaceae isolates, *Citrobacter* is the most common genus identified [41, 42]. In our cases, all *Citrobacter* isolates were resistant to ampicillin and highly resistant to ampicillin/sulbactam as well (Table 2), which is in contrast to the past *Citrobacter* antibiograms. Piperacillin/tazobactam would appear to be a useful alternative, but its intraperitoneal delivery could be problematic, given its incompatibility with aminoglycosides and its potential neurotoxicity [13, 25, 43]. Antibiotic susceptibility among *Citrobacter* species also differs; for example, *C. koseri* has lower antibiotic resistance than *C. freundii* [28, 44]. We also found that *C. koseri* demonstrated higher susceptibility to ampicillin/sulbactam, cefazolin and cefmetazole than *C. freundii* in our study. s. In addition, ineffective empirical antibiotics are associated with higher mortality in *Citrobacter* infections [41]. The most reliable first-line antibiotics for the treatment of PD-related peritonitis caused by *Citrobacter* would be third- or fourth-generation cephalosporins, carbapenems, or fluoroquinolones, with or without aminoglycosides. Consequently, physicians should also be cautious of prescribing penicillin/beta-lactamase inhibitors in cases of PD-related peritonitis caused by *Citrobacter*.

The clinical outcomes in patients with *Citrobacter* infections are often worse than those in patients with other GNB infections; these include high mortality rates (15–55%) [30, 37, 45]. Among patients in the present study, the mortality rate was 18%, similar to the rates in the literature but significantly higher than ones in PD-associated peritonitis caused by other pathogens (<3%) [1, 9]. These adverse outcomes could not be attributed to the slightly shorter duration of antibiotics use (11 days in 2 patients; 18%), since both patients were not hospitalized and were successfully cured by first-line antibiotics. PD-related peritonitis caused by *Citrobacter* is associated with a higher hospital admission rate (54%) and longer hospitalization duration (9 days); these 2 findings are also reported in other non-*Pseudomonas* GNB (NPGNB) peritonitis episodes [7]. However, the mortality rate is significantly higher in PD-related peritonitis caused by *Citrobacter* than in other NPGNB peritonitis episodes (18% vs. 4%) [7], suggesting that *Citrobacter* should be considered separately from the spectrum of NPGNB in terms of peritonitis. The long-term outcomes of patients with PD-related peritonitis caused by *Citrobacter* are also poor, with most patients developing technique failure within 1 year (Table 3), most often caused by infection-related complications (7 cases; 88%). Indeed, the development of *Citrobacter* peritonitis in PD patients serves almost as a warning sign for infection-related technique failure within the following year. These patients should be closely monitored after their recovery from the episode of *Citrobacter* PD peritonitis.

Conclusion

To our knowledge, this study is the first consecutive series of episodes of PD-related peritonitis caused by *Citrobacter* to date, with focused descriptions of their clinical features. Constipation/diarrheas associated origin (potentially GI flora transmural migration) was the most common route of *Citrobacter* peritoneal infection. Patients with PD-related peritonitis caused by *Citrobacter* had high rates of hospitalization and mortality, with high technique failure rates within the upcoming year due to refractory peritonitis.

Acknowledgement

We are grateful to the staffs of the Center of Peritoneal Dialysis in National Taiwan University Hospital (NTUH) for their contributions, the staffs of the Second core lab of the department of Medical Research of NTUH for their technical support, and the financial support from NTUH (project NO.102-N2249).

Conflict of Interest

The authors have no relevant financial or non-financial competing interests to declare in relation to this paper.

References

1. Piraino B. Peritonitis as a complication of peritoneal dialysis. J Am Soc Nephrol. 1998; 9: 1956-64.
2. Adequacy of dialysis and nutrition in continuous peritoneal dialysis: association with clinical outcomes. Canada-USA (CANUSA) Peritoneal Dialysis Study Group. J Am Soc Nephrol. 1996; 7: 198-207.
3. Szeto C-C, Wong TY-H, Leung C-B, et al. Importance of dialysis adequacy in mortality and morbidity of Chinese CAPD patients. Kidney Int. 2000; 58: 400-7.
4. Szeto CC, Leung CB, Chow KM, et al. Change in bacterial aetiology of peritoneal dialysis-related peritonitis over 10 years: experience from a centre in south-east Asia. Clin Microbiol Infect. 2005; 11: 837-9.
5. Kavanagh D, Prescott GJ, Mactier RA, et al. Peritoneal dialysis-associated peritonitis in Scotland (1999–2002). Nephrol Dial Transplant. 2004; 19: 2584-91.
6. Davenport A. Peritonitis remains the major clinical complication of peritoneal dialysis: the London, UK, peritonitis audit 2002–2003. Perit Dial Int. 2009; 29: 297-302.
7. Jarvis EM, Hawley CM, McDonald SP, et al. Predictors, treatment, and outcomes of non-Pseudomonas Gram-negative peritonitis. Kidney Int. 2010; 78: 408-14.
8. Zurowska A, Feneberg R, Warady BA, et al. Gram-Negative Peritonitis in Children Undergoing Long-term Peritoneal Dialysis. Am J Kidney Dis. 2008; 51: 455-62.
9. Szeto CC, Chow VC, Chow KM, et al. Enterobacteriaceae peritonitis complicating peritoneal dialysis: A review of 210 consecutive cases. Kidney Int. 2006; 69: 1245-52.
10. Zelenitsky S, Barns L, Findlay I, et al. Analysis of Microbiological Trends in Peritoneal Dialysis-Related Peritonitis From 1991 to 1998. Am J Kidney Dis. 2000; 36: 1009-13.
11. Sepandj F, Ceri H, Gibb A, et al. Minimum inhibitory concentration (MIC) versus minimum biofilm eliminating concentration (MBEC) in evaluation of antibiotic sensitivity of gram-negative bacilli causing peritonitis. Perit Dial Int. 2004; 24: 65-7.
12. Li PK-T, Szeto CC, Piraino B, et al. Peritoneal dialysis-related infections recommendations: 2010 update. Perit Dial Int. 2010; 30: 393-423.
13. Friedman O, Jassal SV, Bargman JM. Acinetobacter Peritoneal Dialysis Peritonitis: Description and Relation to the SPICE Family of Organisms. Perit Dial Int. 2008; 28: 195-7.
14. Harris PNA, Ferguson JK. Antibiotic therapy for inducible AmpC β-lactamase-producing Gram-negative bacilli: what are the alternatives to carbapenems, quinolones and aminoglycosides? Int J Antimicrob Agent. 2012; 40: 297-305.
15. Wong MY, Lau SKP, Tang SCW, et al. First Report of Peritoneal Dialysis–Related Peritonitis Caused by Citrobacter amalonaticus. Perit Dial Int. 2012; 32: 224-5.
16. Gursu M, Aydin Z, Pehlivanoglu F, et al. Citrobacter peritonitis: two cases and review of the literature. Perit Dial Int. 2011; 31: 409-11.
17. Dervisoglu E, Yumuk Z, Yegenaga I. Citrobacter freundii peritonitis and tunnel infection in a patient on continuous ambulatory peritoneal dialysis. J Med Microbiol. 2008; 57: 125-7.
18. Carlini A, Mattei R, Mazzotta L, et al. Citrobacter braakii, an unusual organism as cause of acute peritonitis in PD patients. Perit Dial Int. 2005; 25: 405-6.
19. Chao CT, Lee SY, Yang WS, et al. Peritoneal dialysis peritonitis by anaerobic pathogens: a retrospective case series. BMC Nephrol. 2013; 14: 111
20. Keane W, Everett E, Golper T, et al. Peritoneal dialysis-related peritonitis treatment recommendations. 1993 update. The Ad Hoc Advisory Committee on Peritonitis Management. International Society for Peritoneal Dialysis. Perit Dial Int. 1993; 13: 14-28.
21. Prowant B, Nolph K, Ryan L, et al. Peritonitis in continuous ambulatory peritoneal dialysis: analysis of an 8-year experience. Nephron. 1986; 43: 105-9.
22. Singharetnam W, Holley J. Acute treatment of constipation may lead to transmural migration of bacteria resulting in gram-negative, polymicrobial, or fungal peritonitis. Perit Dial Int. 1996; 16: 423-5.
23. Kern E, Newman L, Cacho C, et al. Abdominal catastrophe revisited: the risk and outcome of enteric peritoneal contamination. Perit Dial Int. 2002; 22: 323-34.
24. Keane WF, Alexander SR, Bailie GR, et al. Peritoneal dialysis-related peritonitis treatment recommendations: 1996 update. Perit Dial Int. 1996; 16: 557-73.
25. Piraino B, Bailie G, Bernardini J, et al. Peritoneal dialysis-related infections recommendations: 2005 update. Perit Dial Int. 2005; 25: 107-31.
26. Keane W, Bailie G, Boeschoten E, et al. Adult peritoneal dialysis-related peritonitis treatment recommendations: 2000 update. Perit Dial Int. 2000; 20: 396-411.
27. Hodges GR, Degener C, Barnes WG. Clinical significance of citrobacter isolates. Am J Clin Pathol. 1978; 70: 37-40.
28. Drelichman V, Band JD. Bacteremias due to citrobacter diversus and citrobacter freundii: Incidence, risk factors, and clinical outcome. Arch Intern Med. 1985; 145: 1808-10.
29. Samonis G, Karageorgopoulos DE, Kofteridis DP, et al. Citrobacter infections in a general hospital: characteristics and outcomes. Eur J Clin Microbiol Infect Dis. 2009; 28: 61-8.
30. Lavigne JP, Defez C, Bouziges N, et al. Clinical and molecular epidemiology of multidrug-resistant Citrobacter spp. infections in a French university hospital. Eur J Clin Microbiol Infect Dis. 2007; 26: 439-41.
31. Hadley AC, Karchmer TB, Russell GB, et al. The Prevalence of Resistant Bacterial Colonization in Chronic Hemodialysis Patients. Am J Nephrol. 2007; 27: 352-9.
32. Anders H-J, Andersen K, Stecher B. The intestinal microbiota, a leaky gut, and abnormal immunity in kidney disease. Kidney Int. 2013; [Epub ahead of print]
33. Kerri A. Thom MD, Judith A, et al. Increasing Prevalence of Gastrointestinal Colonization With Ceftazidime-Resistant Gram-Negative Bacteria Among Intensive Care Unit Patients. Infect Control Hosp Epidemiol. 2007; 28: 1240-6.
34. Wiest R, Garcia-Tsao G. Bacterial translocation (BT) in cirrhosis. Hepatology. 2005; 41: 422-33.
35. Chao CT, Wu VC, Lai CF, et al. Advanced age affects the outcome-predictive power of RIFLE classification in geriatric patients with acute kidney injury. Kidney Int 2012; 82: 920-7.
36. Mohanty S, Singhal R, Sood S, et al. Citrobacter infections in a tertiary care hospital in Northern India. J Infect. 2007; 54: 58-64.
37. Shih C-C, Chen Y-C, Chang S-C, et al. Bacteremia Due to Citrobacter Species: Significance of Primary Intraabdominal Infection. Clin Infect Dis. 1996; 23: 543-9.
38. Barraclough K, Hawley CM, McDonald SP, et al. Polymicrobial Peritonitis in Peritoneal Dialysis Patients in Australia: Predictors, Treatment, and Outcomes. Am J Kidney Dis. 2010; 55: 121-31.
39. van Esch S, Krediet RT, Struijk DG. Prognostic factors for peritonitis outcome. Contrib Nephrol. 2012; 178: 264-70.
40. Gupta N, Yadav A, Choudhary U, et al. Citrobacter Bacteremia in a Tertiary Care Hospital. Scand J Infect Dis. 2003; 35: 765-8.
41. Pepperell C, Kus JV, Gardam MA, et al. Low-Virulence Citrobacter Species Encode Resistance to Multiple Antimicrobials. Antimicrob Agent Chemother. 2002; 46: 3555-60.
42. Gardam MA, Burrows LL, Kus JV, et al. Is Surveillance for Multidrug-Resistant Enterobacteriaceae an Effective Infection Control Strategy in the Absence of an Outbreak? J Infect Dis. 2002; 186: 1754-60.
43. Lin C-S, Cheng C-J, Chou C-H, et al. Piperacillin/Tazobactam-Induced Seizure Rapidly Reversed by High Flux Hemodialysis in a Patient on Peritoneal Dialysis. Am J Med Sci. 2007; 333: 181-4.
44. Gill MA, Schutze GE. Citrobacter urinary tract infections in children. Pediatr Infect Dis J. 1999; 18: 889-92.
45. Kim BN, Woo JH, Ryu J, et al. Resistance to Extended-Spectrum Cephalosporins and Mortality in Patients with Citrobacter freundii Bacteremia. Infection. 2003; 31: 202-7.