Corynebacterium peritonitis in Australian peritoneal dialysis patients: predictors, treatment and outcomes in 82 cases

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Abstract

Background. Infection due to *Corynebacterium* species has been reported with increasing frequency over recent decades. The impacts of enhanced laboratory detection together with widespread use of new peritoneal dialysis (PD) connection technology and antimicrobial prophylaxis strategies on *Corynebacterium* PD-associated peritonitis have not been well studied.

Methods. We investigated the frequency, predictors, treatment and clinical outcomes of *Corynebacterium* peritonitis in all Australian adult patients involving 66 centres who were receiving PD between 1 October 2003 and 31 December 2006.

Results. Eighty-two episodes of Corynebacterium peritonitis (2.3% of all peritonitis episodes) occurred in 65 (1.4%) PD patients. Ten (15%) patients experienced more than one episode of Corynebacterium peritonitis and additional organisms were isolated in 12 (15%) episodes of Corynebacterium peritonitis. The incidence of Corynebacterium peritonitis was significantly and independently predicted only by BMI: RR 2.72 (95% CI 1.38–5.36) for the highest tertile BMI compared with the lowest tertile. The overall cure rate with antibiotics alone was 67%, which was similar to that of peritonitis due to other organisms. Vancomycin was the most common antimicrobial agent administered in the initial empiric and subsequent antibiotic regimens, although outcomes were similar regardless of antimicrobial schedule. Corynebacterium peritonitis not infrequently resulted in relapse (18%), repeat peritonitis (15%), hospitalization (70%), catheter removal (21%), permanent haemodialysis transfer (15%) and death (2%). The individuals who had their catheters removed more than 1 week after the onset of Corynebacterium peritonitis had a significantly higher risk of permanent haemodialysis transfer than those who had their catheters removed within 1 week (90% versus 43%, P < 0.05).

Conclusions. Corynebacterium is an uncommon but significant cause of PD-associated peritonitis. Complete cure with antibiotics alone is possible in the majority of patients, and rates of adverse outcomes are comparable to those seen with peritonitis due to other organisms. Use of vancomycin rather than cephazolin as empiric therapy does not impact outcomes, and a 2-week course of antibiotic therapy appears sufficient. If catheter removal is required, outcomes are improved by removing the catheter within 1 week of peritonitis onset.

Keywords: antibiotics; corynebacteria; diphtheroids; peritonitis; renal failure

Introduction

Corynebacterium is a genus of gram-positive, facultatively anaerobic, non-motile, irregularly shaped rods [1] that comprise part of the normal skin flora. They live in dynamic equilibrium with other resident gram-positive organisms such as *Staphylococcus* and *Micrococcus sp* [2].

Previously, *Corynebacterium* was thought to have little pathogenic potential in men. However, reporting of infections due to *Corynebacterium* has increased over the past few decades, in large part due to improved recognition of *Corynebacterium* species by microbiologists [1,3]. A wide spectrum of disease has been described, including endocarditis, pulmonary infiltrates, meningitis, soft tissue infections, device-related nosocomial infections, urinary tract infections and septicaemia [1,3–7]. While most infections have involved immunocompromised patients,

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infections in immunocompetent hosts have also been observed [3].

Reports of peritonitis due to Corynebacterium comprise only case reports and small case series from the 1980s and 1990s [8–16]. Additionally, it is unclear whether advances in PD such as widespread use of new connection technology and prophylactic antimicrobial exit site applications may have altered the frequency of PD-associated peritonitis due to Corynebacterium. The optimal treatment strategy is also not well defined. Indeed, current guidelines from the International Society for Peritoneal Dialysis [17] make no mention of peritonitis due to this organism.

The aim of the current study was to examine the frequency, predictors, treatment and clinical outcomes of *Corynebacterium* peritonitis in all Australian PD patients in the current era.

Patients and methods

Study population

The study included all Australian adult patients from the ANZDATA Registry who were receiving PD between 1 October 2003 (when detailed peritonitis data started to be collected) and 31 December 2006. The data collected included demographic data, cause of primary renal disease, comorbidities at the start of dialysis (coronary artery disease, peripheral vascular disease, cerebrovascular disease, chronic lung disease, diabetes, hypertension and smoking status), body mass index (BMI), late referral (defined as commencement of dialysis within 3 months of referral to a nephrologist), microbiology of peritonitis episodes and the initial and subsequent antibiotic treatment regimens. Corynebacterium Peritonitis was defined as clinical features of peritonitis (abdominal pain or cloudy dialysate), dialysate leukocytosis (white blood cell count >100 /μL with >50% neutrophils) and isolation of Corynebacterium or diphtheroids from dialysate culture. In cases of polymicrobial peritonitis, corynebacterial peritonitis was recorded if a Corynebacterium was at least one of the isolated organisms. Centre size was categorized according to quartiles of the numbers of patients cared for by individual units over the duration of the study: small (<11 patients), small-medium (11-38 patients), mediumlarge (39–98 patients) and large (>99 patients).

The outcomes examined were peritonitis relapse, repeat peritonitis, peritonitis-associated hospitalization, catheter removal, temporary or permanent transfer to haemodialysis and patient death. Peritonitis relapse was defined as an episode of peritonitis occurring within 4 weeks of the last antibiotic dose (or within 5 weeks if intermittent vancomycin used) for peritonitis due to the same organism. Repeat peritonitis was defined as an episode of peritonitis occurring more than 4 weeks after the last antibiotic dose (or more than 5 weeks if intermittent vancomycin used) for peritonitis due to the same organism. A peritonitis episode was considered 'cured' by antibiotics alone if the patient was symptom free, the PD effluent was clear and the episode was not complicated by relapse, catheter removal or death. Peritonitis-related death was recorded if the patient's death was directly attributable to peritonitis in the clinical opinion of the treating nephrologist.

Statistical analysis

The results were expressed as frequencies and percentages for categorical variables, mean \pm standard deviation for continuous variables and median and interquartile range for non-parametric data. The differences between two groups of patients were analysed using the chi-square test for categorical data, the unpaired *t*-test for continuous parametric data and the Mann–Whitney test for continuous non-parametric data. The independent predictors of *Corynebacterium* peritonitis incidence were determined by multivariate Poisson regression using backward stepwise elimination. For Poisson analyses, the correlation between observations (intraclass correlation) was taken into account by utilizing a multilevel modelling technique: the hierarchical model took into account clustering based on state of residence, treating unit and individual patient (as patients could have >1

event). The predictors of peritonitis outcomes were determined by multivariate logistic regression using stepwise backward elimination. First-order interaction terms between the significant covariates were examined for all analyses. Data were analysed using the software packages SPSS for Windows release 12.0 (SPSS Inc., North Sydney, Australia) and Stata/SE 10.1 (College Station, TX, USA). The *P*-values <0.05 were considered statistically significant.

Results

Population characteristics

A total of 4675 patients received peritoneal dialysis in Australia during the study period (1 October 2003 to 31 December 2006). They were followed for 6002 patientyears. Eighty-two episodes of Corynebacterium peritonitis occurred in 65 individuals. Corynebacterium peritonitis accounted for 2.3% of all peritonitis episodes. The rates of all peritonitis and Corynebacterium peritonitis were 0.60 and 0.014 episodes per patient-year of treatment, respectively. During the study period, 55 patients experienced one episode of Corynebacterium peritonitis, 5 experienced two episodes, 3 experienced three episodes and 2 experienced four episodes. Additional organisms were isolated in 12 (15%) episodes of Corvnebacterium peritonitis, including coagulase negative staphylococci (n = 3), Streptococcus viridans (n = 1), other gram-positive organisms (n = 5), other gram-negative organisms (n = 1), anaerobic bacteria (n = 1) and atypical mycobacteria (n = 1).

Predictors of Corynebacterium peritonitis

The characteristics of patients who did and did not experience Corynebacterium peritonitis are shown in Table 1. On univariate analysis, patients who experienced Corynebacterium peritonitis during the study period were more likely to be older, but did not significantly differ in any other way from those who did not experience Corynebacterium peritonitis. Using multilevel Poisson regression (to account for intraclass correlations), the incidence of Corynebacterium peritonitis was significantly and independently predicted only by BMI: RR 2.72 (95% CI 1.38-5.36) for the highest tertile BMI compared with the lowest tertile. There was also a non-significant trend to a higher incidence with the middle tertile BMI group. The incidence of Corynebacterium peritonitis was not associated with age, gender, racial origin, kidney function at dialysis commencement, cause of endstage renal failure, chronic lung disease, coronary artery disease, peripheral vascular disease, cerebrovascular disease, diabetes mellitus, smoking status, peritoneal transport status, centre size, state of residence or late referral within 3 months of needing to start dialysis.

Treatment of Corynebacterium peritonitis

The vast majority of patients with polymicrobial peritonitis were initially treated with either intraperitoneal vancomycin or cephazolin in combination with gentamicin as empiric therapy (Table 2). A second antibiotic regimen was introduced in 54% of episodes after a median period of 3 days following peritonitis onset, whilst a third antibiotic regimen was introduced in 11% of patients after a median period of 5 days (Table 3). Vancomycin was the most common

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Table 1. Characteristics of all Australian PD patients who did and did not experience Corynebacterium peritonitis at any stage during the period 2003–2006

Characteristic	Corynebacterium peritonitis ($n = 65$)	No <i>Corynebacterium</i> peritonitis ($n = 4610$)	P-value
Age (years)	65.4 ± 12.4	61.5 ± 16.8	0.05
Women	30 (46%)	2096 (45%)	0.9
Racial origin			0.2
Caucasian	50 (77%)	3531 (77%)	
Aboriginal/Torres Strait islander	3 (5%)	358 (8%)	
Maori/Pacific islander	7 (11%)	104 (2%)	
Asian	4 (6%)	437 (9%)	
Other	5 (8%)	180 (4%)	
BMI (kg/m^2)	27.1 ± 5.0	25.9 ± 6.4	0.13
eGFR at dialysis start (mL/min/1.73 m ²)	6.6 ± 3.2	7.1 ± 4.5	0.3
Late referral	17 (26%)	1094 (24%)	0.6
ESRF Cause			0.9
Chronic glomerulonephritis	18 (28%)	1305 (28%)	
Diabetic nephropathy	16 (25%)	1303 (28%)	
Renovascular disease	9 (14%)	630 (14%)	
Polycystic kidneys	6 (9%)	250 (5%)	
Reflux nephropathy	2 (3%)	195 (4%)	
Other	9 (14%)	636 (14%)	
Unknown	5 (8%)	291 (6%)	
Current smoker	12 (18%)	545 (12%)	0.2
Chronic lung disease	6 (9%)	593 (13%)	0.4
Coronary artery disease	22 (34%)	1645 (36%)	0.8
Peripheral vascular disease	12 (18%)	1034 (22%)	0.4
Cerebrovascular disease	6 (9%)	602 (13%)	0.4
Diabetes mellitus	25 (38%)	1713 (37%)	0.8
Peritoneal transport status			0.08
High	7 (11%)	464 (10%)	
High average	31 (48%)	1680 (36%)	
Low average	17 (26%)	1061 (23%)	
Low	3 (5%)	173 (4%)	
Unknown/not specified	7 (11%)	1210 (26%)	
Centre size (no. of PD patients)			0.4
Small (≤ 10)	0 (01%)	55 (1%)	
Small-medium (11-38)	4 (6%)	317 (7%)	
Medium-large (39–98)	10 (15%)	958 (21%)	
Large (≥99)	51 (78%)	3220 (70%)	
State			0.3
New South Wales	24 (37%)	1808 (39%)	
Northern Territory	1 (2%)	84 (2%)	
Queensland	7 (11%)	948 (21%)	
South Australia	6 (9%)	289 (6%)	
Tasmania	1 (2%)	76 (2%)	
Victoria	20 (31%)	940 (20%)	
Western Australia	6 (9%)	465 (10%)	

antimicrobial agent employed in the 1st, 2nd and 3rd antibiotic regimens. Cephalosporins (predominantly cephazolin and ceftazidime) were the second most common agent administered. Seven of the 11 patients (64%) in whom a third antibiotic regimen was introduced received oral antibiotics, suggesting improvement with, rather than lack of response to, the first two intraperitoneal regimens. The median total duration of antibiotic administration was 13 days (IQR 7–18 days).

Outcomes of Corynebacterium peritonitis

The overall cure rate with antibiotics alone was 67%. Nevertheless, *Corynebacterium* peritonitis episodes not infrequently resulted in relapse (18%), repeat peritonitis (15%), hospitalization (70%), catheter removal (21%), permanent haemodialysis transfer (15%) and death (2%) (Table 3). Following further antibiotic treatment of relapsed peritoni-

tis episodes, the secondary cure rate was 77%. These outcomes were not significantly different to the group outcomes for all peritonitis episodes due to organisms other than Corynebacterium (Table 3). However, Corynebacterium peritonitis was associated with a shorter total antibiotic course duration and longer times to catheter removal and permanent haemodialysis transfer than other forms of peritonitis. Corynebacterium peritonitis outcomes were similar regardless of whether patients were initially treated with vancomycin, cephalosporins or other antimicrobial agents: relapse (17% versus 20% versus 18%, respectively, P = 0.9), hospitalization (58% versus 77% versus 81%, P = 0.14), catheter removal (17% versus 23% versus 27%, P = 0.7), permanent haemodialysis transfer (11% versus 14% versus 27%, P = 0.4) and death (3% versus 14% versus 1sus 3% versus 0%, P = 0.9). The isolation of a second organism in addition to Corynebacterium was associated with a significantly increased probability of catheter removal

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Table 2. Antimicrobial agents prescribed in initial, second and third antibiotic regimens for *Corynebacterium* peritonitis episodes in Australian PD patients 2003–2006

Antibiotic	1st regimen $(n = 82)$	2nd regimen $(n = 38)$	3rd regimen $(n = 9)$
Cephazolin	38 (46%)	4 (11%)	0 (0%)
Vancomycin	36 (44%)	34 (89%)	3 (33%)
Gentamicin	50 (61%)	8 (21%)	0 (0%)
Cephalothin	5 (6%)	1 (3%)	1 (11%)
Ceftazidime	15 (18%)	0 (0%)	0 (0%)
Ceftriaxone	2 (2%)	2 (5%)	0 (0%)
Other cephalosporin	8 (10%)	0 (0%)	0 (0%)
Other aminoglycoside	0 (0%)	0 (0%)	0 (0%)
Amoxicillin/ampicillin	0 (0%)	0 (0%)	4 (44%)
Flucloxacillin/dicloxacillin/cloxacillin	1 (1%)	0 (0%)	0 (0%)
Carbapenem	0 (0%)	0 (0%)	0 (0%)
Metronidazole	0 (0%)	1 (3%)	1 (11%)
Ciprofloxacin	3 (4%)	2 (5%)	1 (11%)
Teicoplanin	0 (0%)	0 (0%)	0 (0%)
Rifampicin	1 (1%)	0 (0%)	0 (0%)
Sulphamethoxazole-Trimethoprim	0 (0%)	2 (5%)	0 (0%)
Antifungal agent	0 (0%)	0 (0%)	0 (0%)
Ticarcillin	0 (0%)	0 (0%)	2 (22%)
Erythromycin	2 (2%)	0 (0%)	0 (0%)

Results represent number of episodes treated with antibiotic (% of total treated with 1st, 2nd or 3rd line regimen). Note that values within each column add to more than 100% because of the use of combination antimicrobial regimens.

Table 3. Treatment characteristics and clinical outcomes of PD-associated Corynebacterium peritonitis in Australia 2003–2006

Outcome	Corynebacterium peritonitis $(n = 82 \text{ episodes})$	Non-Corynebacterium peritonitis $(n = 3512 \text{ episodes})$	P-value
Treatment			
Change to 2nd antibiotic regimen	44 (54%)	1966 (56%)	
Time to 2nd antibiotic regimen	3 [2–4]	3 [2–5]	0.8
Change to 3rd antibiotic regimen	9 (11%)	488 (14%)	
Time to 3rd antibiotic regimen	5 [3–19]	6 [4–10]	0.5
Total antibiotic treatment duration	13 [7–18]	14 [8–20]	0.08
Relapse	15 (18%)	487 (14%)	0.3
Hospitalisation	` /	` '	
Number (%)	57 (70%)	2447 (70%)	1.0
Duration (days)	7 [3.5–14.5]	6 [3–12]	0.4
Catheter removal			
Number (%)	17 (21%)	758 (22%)	0.9
Time to occurrence (days)	10[6–21]	6 [3–13]	0.03
Temporary haemodialysis		· ·	
Number (%)	6 (7%)	146 (4%)	0.16
Time to occurrence (days)	8 [2.25–11.5]	6 [3–12]	1.0
Duration (days)	61.5 [6.25–98.5]	67 [24–104]	0.8
Permanent haemodialysis	-	-	
Number (%)	12 (15%)	623 (18%)	0.5
Time to occurrence	12.5 [8.5–33.5]	7 [4–12]	0.008
Death			
Number (%)	2 (2%)	80 (2%)	0.9
Time to death	Days 1 & 15	12 [4–24]	0.5

Results are expressed as number (%) or median days [interquartile range].

(42% versus 17%, P = 0.05) and permanent haemodialysis transfer (42% versus 10%, P = 0.004) compared with pure *Corynebacterium* peritonitis. Compared with patients who had their catheters removed within 1 week of the onset of *Corynebacterium* peritonitis (n = 7), the 10 individuals who had their catheters removed after more than 1 week had a significantly higher risk of permanent haemodialysis transfer (90% versus 43%, P < 0.05). No deaths occurred amongst patients who had their catheters removed for *Corynebacterium* peritonitis.

Using binary logistic regression, age was a significant, independent predictor of hospitalization (OR 1.07, 95% CI 1.00–1.15), as was the presence of chronic lung disease (OR 92.0, 95% CI 1.95–4330) and the administration of cephalosporins (OR 6.83, 95% CI 1.00–47.0) or an agent other than vancomycin in the initial, empiric antibiotic regimen (OR 30.8, 95% CI 1.17–809). Increasing BMI tended to predict an increased risk of *Corynebacterium* peritonitis relapse (OR 1.61, 95% CI 0.97–2.67) and polymicrobial peritonitis tended to be associated

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with permanent haemodialysis transfer (OR 19.8, 95% CI 0.84–465, P = 0.064). There were no other independent predictors of *Corynebacterium* peritonitis outcomes (relapse, hospitalization, catheter removal, permanent haemodialysis transfer or death).

Discussion

The present study represents the largest examination to date of the frequency, predictors, treatment and clinical outcomes of PD-associated *Corynebacterium* peritonitis. *Corynebacterium* was found to account for 2.3% of all PD-related peritonitis episodes, and higher BMI independently predicted its incidence. Despite shorter total antibiotic course, the overall cure rate with antibiotics alone was 67%. Vancomycin was the most commonly prescribed antibiotic in the initial empiric and subsequent antimicrobial regimens, although outcomes were generally comparable regardless of which antibiotic was administered. In the minority of patients who had their catheters removed during a *Corynebacterium* peritonitis episode, those whose catheters were removed after more than 1 week had a significantly higher risk of permanent haemodialysis transfer.

The results of our investigation are in keeping with previous findings by Szeto et al. [8] who reported 27 episodes of Corynebacterium peritonitis in 27 patients at a single centre in Hong Kong between 1995 and 2002. Similar to our findings, Szeto et al. observed that Corynebacterium peritonitis accounted for 1.8% of all peritonitis episodes. This was despite only 16 of 27 patients using disconnect PD systems, compared with all patients in our more contemporary cohort. The investigators also observed a similar primary response rate (74.1%) to antibiotic therapy, as well as a similar relapse rate (18%) following completion of antibiotic treatment. However, in contrast with our findings, they found that a markedly higher proportion of Corynebacterium peritonitis episodes resulted in repeat peritonitis (30%). In our study, vancomycin was the most common antimicrobial agent employed in the 1st, 2nd and 3rd antibiotic regimens. While Szeto et al. commented that they followed standard guidelines for antibiotic dosage, they did not report the treatment regimens actually utilized. Thus, it is conceivable that the higher rate of repeat peritonitis in their study may have reflected different antibiotic choice or treatment duration. This is particularly relevant, given that neither study provided data regarding identification of Corvnebacterium to the species level. While antibiotic susceptibility patterns of Corynebacterium have not been studied systematically [1], it is known that some Corynebacterium species are more antibiotic resistant (e.g. C. jeikeium), with most reported strains resistant to all antibiotics except vancomycin [1,3]. This raises the possibility that a higher proportion of episodes in the study by Szeto et al. were due to more resistant species [1]. However, the investigators did report that rates of primary response and complete cure were not lower in the episodes caused by penicillin-resistant strains [8].

An alternative explanation may lie in the predominant (>80%) utilization of PD as a renal replacement therapy in Hong Kong, where haemodialysis transfer occurs as a last resort such that patients are 'switched to haemodialysis only

when they have ultrafiltration failure or peritoneal sclerosis' [18]. This makes it probable that the high relapse rate may in part reflect attempts to prioritize technique survival over cure of peritonitis episode. Consistent with this notion, Szeto *et al.* saw markedly lower rates of catheter removal (14.8%) and permanent haemodialysis transfer (3.7%).

In the study by Szeto et al. [8], primary response and complete cure rates were marginally higher in those that received vancomycin rather than cephalosporins as part of the initial antibiotic regimen, although the difference was not statistically significant. They also reported successful treatment of a substantial number of recurrent episodes with a prolonged course of vancomycin. This led to the suggestion that a 3-week course of vancomycin should be the preferred therapy for Corynebacterium peritonitis, irrespective of antibiotic sensitivity [8]. We found that rates and timing of relapse, hospitalization, catheter removal, haemodialysis transfer and death were similar on univariate analysis regardless of whether patients were initially treated with vancomycin, cephalosporins or other antimicrobial agents. While initial administration of an agent other than vancomycin did independently predict hospitalization on multivariate analysis, it is probable this reflected bias by indication, since the need for more frequent administration of cephazolin is more suited to inpatient treatment whilst the intermittent nature of vancomycin dosing every 5-7 days lends itself more readily to management of peritonitis in the ambulatory setting. Our results would therefore support use of cephazolin rather than vancomycin as empiric therapy so as to avoid development of inadvertent resistance. Further, the comparable rates of relapse and other clinical outcomes seen with Corynebacterium peritonitis and non-Corynebacterium peritonitis in our study occurred despite a median total duration of antibiotic administration of 13 days. This suggests that a 2-week course of antibiotic therapy is sufficient.

Another novel finding from our study was that Corynebacterium peritonitis was associated with shorter total antibiotic course duration and longer times to catheter removal and permanent haemodialysis transfer than other forms of peritonitis. Given that outcomes of Corvnebacterium and non-Corynebacterium peritonitis were comparable, the shorter antibiotic course suggests that Corynebacterium peritonitis may be more easily treated than peritonitis due to other organisms. However, we also found a significantly higher risk of permanent haemodialysis transfer in those patients who had their catheters removed more than 1 week after the onset of Corynebacterium peritonitis compared with those who had their catheters removed within 1 week (90% versus 43%, P < 0.05). Subsequently, decisions to delay catheter removal on the grounds that Corynebacterium may be easier to eradicate should be made with caution.

The strengths of this study include its very large sample size and inclusiveness. We examined all patients receiving PD in Australia during the study period, such that a variety of centres were involved with varying approaches to the treatment of peritonitis. This greatly enhanced the external validity of our findings. These strengths should be balanced against the study's limitations, which include limited depth of data collection. ANZDATA does not collect

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important information such as the type and severity of peritonitis symptoms, presence of concomitant exit site and tunnel infections, patient compliance, individual unit management protocols, laboratory values (such as C-reactive protein and dialysate white cell counts), severity of comorbidities, antibiotic dosages, routes of antibiotic administration, *Corynebacterium* species or antimicrobial susceptibilities or severity of peritonitis symptoms. Even though we adjusted for a large number of patient characteristics, residual confounding may exist. In common with other Registries, ANZDATA is a voluntary Registry and there is no external audit of data accuracy, including the diagnosis of peritonitis. Consequently, the possibility of coding/classification bias cannot be excluded.

In conclusion, Corvnebacterium is an uncommon but significant cause of PD-associated peritonitis. Complete cure with antibiotics alone is possible in the majority of patients, and rates of adverse outcomes are comparable to those seen with peritonitis due to other organisms. However, these rates of adverse outcomes were achieved despite shorter duration of antibiotic administration, and were not worsened by the use of an agent other than vancomycin in the initial empiric antibiotic regimen. This data suggest that Corynebacterium may be a less virulent cause of PD peritonitis. We would recommend treatment with cephazolin rather than vancomycin as empiric therapy, with a total antibiotic treatment duration of 2 weeks if the patient is clinically improving. However, caution should be employed in delaying catheter removal given its association with higher likelihood of permanent transfer to haemodialysis.

Acknowledgements. The authors gratefully acknowledge the substantial contributions of the entire Australia and New Zealand nephrology community (physicians, surgeons, database managers, nurses, renal operators and patients) in providing information for and maintaining the ANZDATA Registry database.

Conflict of interest statement. None declared.

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Received for publication: 5.3.09; Accepted in revised form: 8.6.09