Predictors, treatment, and outcomes of non-Pseudomonas Gram-negative peritonitis

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Non-Pseudomonas Gram-negative (NPGN) peritonitis is a frequent, serious complication of peritoneal dialysis; however, previous reports have been limited to small, single-center studies. To gain insight on the frequency, predictors, treatment, and outcomes of NPGN peritonitis, we analyzed data in the ANZDATA registry of all adult Australian peritoneal dialysis patients over a 39-month period using multivariate logistic and multilevel Poisson regressions. There were 837 episodes of NPGN peritonitis (23.3% of all peritonitis) that occurred in 256 patients. The most common organism isolated was *Escherichia coli*, but included *Klebsiella*, *Enterobacter*, *Serratia*, *Acinetobacter*, *Proteus*, and *Citrobacter*, with multiple organisms identified in a quarter of the patients. The principal risk factor was older age, with poorer clinical outcome predicted by older age and polymicrobial peritonitis. The overall antibiotic cure rate was 59%. NPGN peritonitis was associated with significantly higher risks of hospitalization, catheter removal, permanent transfer to hemodialysis, and death compared to other organisms contributing to peritonitis. Underlying bowel perforation requiring surgery was uncommon. Hence, we show that NPGN peritonitis is a frequent, serious complication of peritoneal dialysis, which is frequently associated with significant risks, including death. Its cure with antibiotics alone is less likely when multiple organisms are involved.

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Peritonitis is a serious complication of peritoneal dialysis (PD), accounting for 30% of technique failures and 21% of infectious deaths in Australian and New Zealand PD patients.[1] The overall rates of peritonitis have decreased since the early 1990s[1–3] because of advances in connectology and *Staphylococcus* decolonization protocols.[2,4–6] These improvements have primarily made an impact on the incidence of Gram-positive peritonitis, in such a manner that the proportion of PD-associated infections due to Gram-negative organisms has consequently increased.[2–4] Available data suggest that non-Pseudomonas Gram-negative (NPGN) organisms now account for approximately 20–30% of all peritonitis episodes, are often more severe than other forms of PD-associated peritonitis, and are associated with worse clinical outcomes, including catheter loss, technique failure, and death.[2,3,7–9]

The 2005 update of the International Society of PD (ISPD) Guidelines for Management of PD-related Infections recommends treatment of NPGN peritonitis with an appropriate single antimicrobial agent (for example, aminoglycoside, ceftazidime, cefepime, carbapenem, or quinolone), based on *in vitro* antibiotic sensitivity testing, for a period of 3 weeks.[9] However, these recommendations are based on limited earlier data from small, retrospective, often single-center observational cohort studies.[7,10] There has not been a comprehensive examination of different therapeutic approaches to NPGN peritonitis across multiple centers. Moreover, a more recent, single-center study from Hong Kong suggested that single-agent antibiotic therapy was associated with an increased risk of *Enterobacteriaceae* peritonitis relapse compared with dual antibiotic therapy.[3]

The aim of the current study was to examine the frequency, predictors, treatment, and clinical outcomes of NPGN peritonitis in all Australian PD patients involving 66 PD centers.

RESULTS

Population characteristics

A total of 4675 patients received PD in Australia during the study period (1 October 2003 to 31 December 2006).

They were followed up for 6002 patient-years. Eight hundred and thirty-seven episodes of NPGN peritonitis occurred in 256 individuals. NPGN species accounted for 23.3% of all the 3594 peritonitis episodes. The rate of NPGN peritonitis was 0.14 episodes per patient-year of treatment. The causes of single-organism NPGN peritonitis ($n=626$) were *Acinetobacter* ($n=45$), *E. coli* ($n=206$), *Klebsiella* ($n=128$), *Enterobacter* ($n=74$), *Serratia* ($n=69$), *Proteus* ($n=23$), *Citrobacter* ($n=14$), other *Enterobacteriaceae* ($n=2$), *Neisseria* ($n=9$), and other Gram-negative organisms ($n=56$). Multiple organisms were isolated in 211 (25%) episodes of NPGN peritonitis, including coagulase-negative staphylococci ($n=24$), *Staphylococcus aureus* ($n=13$), *Enterococci* ($n=29$), other Gram-positive organisms ($n=7$), *Pseudomonas* ($n=26$), *Acinetobacter* ($n=21$), *E. coli* ($n=79$), *Klebsiella* ($n=61$), *Enterobacter* ($n=39$), *Serratia* ($n=10$), *Proteus* ($n=18$), *Citrobacter* ($n=12$), other *Enterobacteriaceae* ($n=12$), *Neisseria* ($n=5$), other Gram-negative organisms ($n=33$), anaerobic bacteria ($n=4$), fungi ($n=22$), and other organisms ($n=21$). One hundred and seventy-four episodes of peritonitis were associated with 2 organisms, and 37 episodes were associated with 3 organisms. Five hundred and twenty-eight patients experienced 1 episode of NPGN peritonitis during the study period, 90 experienced 2 episodes, 27 experienced 3 episodes, 7 experienced 4 episodes, 2 experienced 5 episodes, and 1 experienced 6 episodes.

Underlying bowel perforations due to diverticular disease, bowel infarction, hernia incarceration, or appendicitis were reported in a small proportion of patients, but were significantly more common in NPGN peritonitis episodes than in other peritonitis episodes (9 or 1.1% vs 3 or 0.1%, $P<0.001$, odds ratio (OR) 10.0, 95% confidence interval (CI) 2.70–36.9). Bowel perforation was significantly more common in polymicrobial than in single-organism NPGN peritonitis (5 or 2.4% vs 4 or 0.6%, $P<0.05$, OR 3.77, 95% CI 1.004–14.2).

Predictors of NPGN peritonitis

The characteristics of patients who did and who did not experience NPGN peritonitis are shown in Table 1. On univariate analysis, patients who experienced NPGN peritonitis during the study period were more likely to be older, of Aboriginal and Torres Strait Islander racial origin, Maori and Pacific Islander racial origin, Asian racial origin, non-diabetic, and to have a baseline PET showing a higher peritoneal transport status or living in New South Wales. Using multivariate, multilevel mixed-effects Poisson regression analysis, the occurrence of NPGN peritonitis was significantly and independently predicted by older age (youngest tertile reference; middle tertile adjusted OR 1.15, 95% CI 0.92–1.44; oldest tertile OR 1.68, 95% CI 1.34–2.11) and ESRF due to diabetic nephropathy (OR 0.66, 95% CI 0.52–0.83). There was a trend to increased occurrence of NPGN peritonitis in females (OR 1.16, 95% CI 0.98–1.38), but this did not achieve statistical significance ($P=0.08$). The development of NPGN peritonitis was not associated with racial origin, BMI, kidney function at dialysis commencement, current smoking status, coronary artery disease, chronic lung disease, cerebrovascular disease, peripheral vascular disease, peritoneal transport status, or late referral within 3 months of needing to start dialysis. The findings were unchanged when only single-organism peritonitis episodes were considered.

Effect of previous peritonitis episodes on occurrence of NPGN peritonitis

A history of previous peritonitis was significantly more common for NPGN than for other peritonitis episodes (89 vs 31%, $P<0.001$). The time elapsed between an earlier peritonitis episode and the subsequent one was not significantly different between NPGN peritonitis (median period 77 days, interquartile range (IQR) 37–185 days) and other forms of peritonitis (median period 80 days, IQR 29.25–172.25 days, $P=0.3$). Consequently, the probability of an episode of subsequent peritonitis being caused by an NPGN species as opposed to another organism remained constant over time (21% in the first 60 days, 22% in the first year, 22% after the first year, $P=1.0$).

Treatment of NPGN peritonitis

The vast majority of patients with NPGN peritonitis were initially treated with either intraperitoneal vancomycin or cephazolin in combination with gentamicin as empirical therapy (Table 2). Once culture results became known at a median time of 3 days, approximately two-thirds of the patients were changed to a second antibiotic regimen, the most common of which were gentamicin monotherapy (14%), ciprofloxacin monotherapy (10%), and ceftriaxone monotherapy (5%). Of those peritonitis episodes in which a second antibiotic regimen was used, 382 (71%) involved treatment with a single antimicrobial agent, 136 (25%) involved two agents, and 21 (4%) involved three agents. Patients were changed to a third antibiotic regimen in 21% of the episodes after a median period of 7 days. Overall, the median total antibiotic course duration was 14 days, which was slightly but significantly longer than for all the other organisms (Table 3). Heparin was administered to the dialysate in 178 (21%) episodes of NPGN peritonitis. Streptokinase was instilled in the PD catheter in 5 (1%) episodes of NPGN peritonitis and only 59 (7%) patients with NPGN peritonitis received concomitant prophylactic nystatin therapy.

Outcomes of NPGN peritonitis

The overall cure rate for NPGN peritonitis was 59%. Compared with other organisms, NPGN peritonitis was associated with significantly lower risks of relapse (11 vs 15%), but higher risks of hospitalization (81 vs 66%), catheter removal (31 vs 19%), permanent hemodialysis transfer (26 vs 15%), and death (4 vs 2%) (Table 3). NPGN peritonitis was also associated with a longer duration of hospitalization (Table 3). No cases of encapsulating peritoneal sclerosis (EPS) after NPGN peritonitis were reported.

Table 1 | Characteristics of all Australian PD patients who did and who did not experience non-Pseudomonas Gram-negative peritonitis at any stage during the period 2003–2006

Characteristic	Non-Pseudomonas Gram-negative peritonitis (*n*=655)	No non-Pseudomonas Gram-negative peritonitis (*n*=4020)	*P* value
Age (years)	64.1 ± 15.9	61.1 ± 16.8	<0.001
Women	338 (52%)	2211 (55%)	0.11
Racial origin			*0.049*
Caucasian	476 (73%)	3105 (77%)	
Aboriginal/Torres Strait Islander	58 (9%)	303 (8%)	
Maori/Pacific Islander	17 (3%)	90 (2%)	
Asian	80 (12%)	361 (9%)	
Other	24 (4%)	161 (4%)	
BMI (kg/m^2)	25.7 ± 5.3	25.9 ± 6.5	0.4
eGFR at dialysis start (ml/min per 1.73 m^2)	7.0 ± 5.5	7.1 ± 4.3	0.5
Late referral	156 (24%)	955 (24%)	0.8
ESRF cause			*0.3*
Chronic glomerulonephritis	192 (29%)	1131 (28%)	
Diabetic nephropathy	160 (24%)	1159 (29%)	
Renovascular disease	96 (15%)	543 (14%)	
Polycystic kidneys	45 (7%)	211 (5%)	
Reflux nephropathy	27 (4%)	170 (4%)	
Other	90 (14%)	555 (14%)	
Unknown	45 (7%)	251 (6%)	
Current smoker	75 (11%)	482 (12%)	0.7
Chronic lung disease	81 (12%)	518 (13%)	0.7
Coronary artery disease	247 (38%)	1420 (35%)	0.2
Peripheral vascular disease	131 (20%)	915 (23%)	0.12
Cerebrovascular disease	73 (11%)	535 (13%)	0.13
Diabetes mellitus	219 (33%)	1519 (38%)	0.03
Peritoneal transport status			*<0.001*
High	81 (12%)	390 (10%)	
High average	248 (38%)	1463 (36%)	
Low average	169 (26%)	909 (23%)	
Low	30 (5%)	168 (4%)	
Unknown/not specified	127 (19%)	1090 (27%)	
Centre size (no. of PD patients)			*0.3*
Small (⩽10)	4 (1%)	51 (1%)	
Small–medium (11–38)	43 (7%)	278 (7%)	
Medium–large (39–98)	135 (21%)	893 (22%)	
Large (⩾99)	473 (72%)	2798 (70%)	
State			*0.001*
New South Wales	291 (44%)	1541 (38%)	
Northern Territory	18 (3%)	67 (2%)	
Queensland	110 (17%)	845 (21%)	
South Australia	30 (3%)	265 (7%)	
Tasmania	7 (1%)	70 (2%)	
Victoria	121 (18%)	839 (21%)	
Western Australia	78 (12%)	393 (10%)	

Abbreviation: PD, peritoneal dialysis.

Table 2 | Antimicrobial agents prescribed in the initial, second, and third antibiotic regimens for NPGN peritonitis episodes in Australian PD patients, 2003–2006

Antibiotic	First regimen (*n*=837)	Second regimen (*n*=539)	Third regimen (*n*=173)
Cephazolin	332 (40%)	59 (11%)	9 (5%)
Vancomycin	355 (42%)	76 (14%)	16 (9%)
Gentamicin	649 (78%)	229 (42%)	40 (23%)
Amikacin	3 (0.4%)	3 (1%)	1 (1%)
Tobramycin	0 (0%)	0 (0%)	1 (1%)
Ceftazidime	76 (9%)	12 (2%)	2 (1%)
Cefoxitin	15 (2%)	6 (1%)	2 (1%)
Cefipime	7 (1%)	1 (0.2%)	0 (0%)
Cephalothin	63 (8%)	18 (3%)	3 (2%)
Ceftriaxone	20 (2%)	53 (10%)	13 (8%)
Cefotaxime	6 (1%)	17 (3%)	4 (2%)
Cephalexin	25 (3%)	22 (4%)	11 (6%)
Other cephalosporin	2 (0.2%)	0 (0%)	0 (0%)
Ampicillin	3 (0.4%)	8 (1%)	3 (2%)
Amoxycillin	4 (0.5%)	12 (2%)	10 (6%)
Amoxycillin+clavulanate	21 (3%)	12 (2%)	9 (5%)
Dicloxacillin/Flucloxacillin	4 (0.5%)	3 (1%)	2 (1%)
Other penicillin	2 (1%)	2 (1%)	0 (0%)
Ciprofloxacin	55 (7%)	98 (18%)	65 (38%)
Metronidazole	11 (2%)	28 (5%)	16 (9%)
Cotrimoxazole	0 (0%)	4 (1%)	6 (3%)
Erythromycin	1 (0.1%)	1 (0.2%)	1 (1%)
Antifungal agent	17 (2%)	13 (2%)	14 (8%)
Imipenem	1 (0.1%)	0 (0%)	0 (0%)
Piperacillin	0 (0%)	7 (1%)	2 (1%)
Ticarcillin	5 (0.6%)	10 (2%)	4 (2%)
Other	13 (2%)	19 (4%)	7 (4%)

Abbreviation: PD, peritoneal dialysis.
Results represent the number of episodes treated with antibiotic (% of total treated with the first-, second-, or third-line regimen). Note that values within each column add to more than 100% because of the use of combination antimicrobial regimens.

The outcomes of peritonitis due to NPGN organisms vs other organisms were similar when single-organism and polymicrobial peritonitis episodes were separately considered (Table 4). Compared with single-organism peritonitis, polymicrobial episodes were associated with greater frequency of changes to second and third antimicrobial regimens and increased occurrences of hospitalization, catheter removal, permanent hemodialysis transfer, and death (Table 4).

The administration of vancomycin, cephalosporin, or any other agent in the initial or subsequent empirical antibiotic regimens did not significantly influence NPGN peritonitis outcomes on either univariate or multivariate analyses. Similarly, the Gram-negative cover used (aminoglycoside or any other agent) did not significantly influence the NPGN peritonitis outcomes. When catheter removal was required to treat NPGN peritonitis, removal of the catheter within the first 5 days of peritonitis onset as opposed to later did not significantly affect the probabilities of either permanent hemodialysis transfer (83 vs 83%, respectively, $P=0.9$) or death (4.5 vs 5.7%, $P=0.9$). Similar results were obtained when only episodes of single NPGN organism peritonitis were considered (permanent hemodialysis transfer 83 vs 81%, $P=0.9$; death 4.6 vs 4.7%, $P=0.7$).

On using multivariable, multilevel mixed-effects logistic regression, isolation of multiple organisms in NPGN peritonitis was associated with increased risks of catheter removal (OR 3.28, 95% CI 2.17–4.96) and permanent

Table 3 | Treatment characteristics and clinical outcomes of PD-associated peritonitis due to non-Pseudomonas Gram-negative or other organisms in Australia, 2003–2006

Outcome	Non-Pseudomonas Gram-negative peritonitis (*n*=837 episodes)	Other organism peritonitis (*n*=2757 episodes)	*P* value
Treatment			
Change to second antibiotic regimen	539 (64%)	1471 (53%)	<0.001
Time to second antibiotic regimen	3 (1–5)	3 (2–5)	0.06
Change to third antibiotic regimen	173 (15%)	324 (12%)	<0.001
Time to third antibiotic regimen	6 (4–9)	7 (4–10)	0.12
Total antibiotic treatment duration	14 (10–21)	14 (8–19)	<0.001
Relapse	91 (11%)	411 (15%)	0.003
Hospitalization			
Number (%)	679 (81%)	1825 (66%)	<0.001
Duration (days)	7 (4–14)	6 (3–11)	<0.001
Catheter removal			
Number (%)	275 (31%)	518 (19%)	<0.001
Time to occurrence (days)	6 (3–10)	6 (3–15)	0.12
Temporary hemodialysis			
Number (%)	34 (4%)	118 (4%)	0.8
Time to occurrence (days)	6 (2.5–9.5)	6.5 (3–13)	0.3
Duration (days)	64 (24–88.5)	68.5 (22.5–104.75)	0.4
Permanent hemodialysis			
Number (%)	219 (26%)	416 (15%)	<0.001
Time to occurrence	7 (4–11)	7 (4–12)	0.3
Death			
Number (%)	35 (4%)	47 (2%)	<0.001
Time to death	11.5 (2–19)	12 (5–25)	0.4

Abbreviation: PD, peritoneal dialysis.
Results are expressed as number (%) or median days (interquartile range).

hemodialysis transfer (OR 2.85, 95% CI 1.88–4.33). Relapse of NPGN peritonitis was less likely associated with polymicrobial peritonitis (OR 0.16, 95% CI 0.53–0.46), although this likely reflected the competing risks, as polymicrobial peritonitis was also associated with catheter removal and permanent hemodialysis transfer. As the number of deaths was only 23 in the NPGN peritonitis cohort, multivariate analysis of the predictors of death was not possible. Increasing age was predictive of hospitalization for NPGN peritonitis (youngest tertile reference; middle tertile OR 2.10, 95% CI 0.99–4.39; oldest tertile OR 3.15, 95% CI 1.48–6.70). Patients with renovascular disease were less likely to undergo permanent hemodialysis transfer (OR 0.49, 95% CI 0.26–0.93): this may relate to a bias towards attempting to avoid long-term hemodialysis in this group, which generally have widespread vascular disease.

DISCUSSION

The present study, involving 837 cases of PD-associated NPGN peritonitis across 66 different PD centers, represents the largest examination to date of the frequency, predictors, treatment, and clinical outcomes of this important condition. NPGN peritonitis accounted for 23% of all peritonitis episodes and was polymicrobial in 25% of cases. Underlying bowel perforation was uncommon (1.1%) but was significantly more likely in polymicrobial NPGN peritonitis (2.4 vs 0.6%). The significant independent predictors of NPGN peritonitis were older age and absence of diabetic nephropathy. Despite treatment with a single antimicrobial agent in the majority of cases for a relatively short median duration of 2 weeks, cure was achieved in 59% of them. Compared with other organisms, NPGN peritonitis was associated with significantly higher risks of hospitalization, catheter removal, permanent hemodialysis transfer, and death. Polymicrobial NPGN peritonitis was a potent predictor of catheter removal, and permanent hemodialysis transfer.

Although the predictors of NPGN peritonitis have not been previously examined and reported, the association of this condition with older age in our study most likely represents the frequent occurrence of underlying gastrointestinal pathology, such as diverticular disease, in the elderly. Interestingly, the presence of diabetic nephropathy was associated with a reduced risk of development of NPGN peritonitis. The reason for this finding is unexplained, although it could reflect competing risks, as we have previously shown that patients with diabetic nephropathy are more prone to Gram-positive peritonitis, particularly due to *S. aureus*.[11]

The results of our study are broadly comparable to those of Szeto *et al.*,[3] who examined 210 consecutive cases of *Enterobacteriaceae* PD-associated peritonitis at a single Hong Kong center from 1995 to 2004. Overall cure was achieved with antibiotics alone in 58% of the episodes (cf. 59% in our study), although the relapse rates (36 vs 11%) and death rates (10 vs 4%) were both considerably higher than found in our study. Part of the apparent disparity in results could be explained by the predominant (>80%) use of PD as a renal replacement therapy in Hong Kong, whereby hemodialysis transfer occurred as a last resort, such that patients were 'switched to hemodialysis only when they have ultrafiltration failure or peritoneal sclerosis'.[3] This makes it probable that the high relapse rate could have in part reflected an attempt to prioritize the technique survival over cure of peritonitis episode. Consistent with this notion, Szeto *et al.*[3] reported markedly lower rates of catheter removal (8 vs 31%) and permanent hemodialysis transfer (1.4 vs 26%) than in our study. An alternative possibility is that a higher proportion of episodes in the study by Szeto *et al.* were due to more resistant species. This is supported by the fact that Szeto *et al.* observed an increase in antibiotic resistance in isolated *Enterobacteriaceae* over time, an increase in the risk of adverse outcomes with prior antibiotic therapy, and an increase in the risk of relapse with single vs dual antibiotic therapy.

Table 4 | Treatment characteristics and clinical outcomes of PD-associated peritonitis due to NPGN organisms or other organisms (non-NPGN) in single-organism and polymicrobial infections in Australia, 2003–2006

	Single-organism peritonitis			Polymicrobial peritonitis		
Outcome	NPGN (*n*=626)	Non-NPGN (*n*=2609)	*P* value	NPGN (*n*=211)	Non-NPGN (*n*=148)	*P* value
Treatment						
Change to second antibiotic regimen	242 (39%)	1365 (52%)	<0.001	155 (73%)	106 (72%)	0.8
Time to second antibiotic regimen	2 (1–5)	3 (2–5)	0.12	3 (1–5)	3 (2–6)	0.08
Change to third antibiotic regimen	101 (16%)	293 (11%)	<0.001	72 (34%)	31 (21%)	0.009
Time to third antibiotic regimen	6 (3.5–9)	7 (4–10)	0.02	6 (4–13)	6 (5–11)	0.7
Total antibiotic treatment duration	14 (9–20)	14 (8–19)	0.2	16 (11–23)	14 (7.75–21)	0.06
Relapse	81 (13%)	386 (15%)	0.2	10 (5%)	25 (17%)	<0.001
Hospitalization						
Number (%)	498 (80%)	1709 (66%)	<0.001	181 (86%)	116 (78%)	0.07
Duration (days)	6 (3–11)	5 (3–11)	0.10	10 (5–20.5)	7 (3–15.5)	0.005
Catheter removal						
Number (%)	152 (24%)	468 (18%)	<0.001	105 (50%)	50 (34%)	0.003
Time to occurrence (days)	6 (3–10)	6 (3–14)	0.4	6 (4–10)	10 (5–21)	0.003
Temporary hemodialysis						
Number (%)	23 (4%)	110 (4%)	0.5	11 (5%)	8 (5%)	0.9
Time to occurrence (days)	5.5 (2–10.25)	7 (3–12.75)	0.3	6 (4–7)	4.5 (1.5–21.25)	0.9
Duration (days)	54 (25.5–79.75)	68.5 (22.5–104)	0.3	74 (17–118)	85 (31.5–144)	0.6
Permanent hemodialysis						
Number (%)	129 (21%)	368 (14%)	<0.001	90 (43%)	48 (32%)	0.05
Time to occurrence	7 (4–10)	7 (4–13.75)	0.5	6 (4–11.5)	10 (6–18)	0.01
Death						
Number (%)	23 (4%)	45 (2%)	0.002	12 (6%)	2 (1%)	0.04
Time to death	8 (1–15.5)	12 (5–24)	0.2	15.5 (5.5–26)	35 (3–158.5)	0.5

Abbreviations: NPGN, non-Pseudomonas Gram-negative; PD, peritoneal dialysis.
Results are expressed as number (%) or median days (interquartile range).

Our results are also in keeping with those of Bunke *et al.*[7] who reported similar rates of cure (58.8%), catheter removal (30%), and death (3.7%) following 136 episodes of NPGN PD-related peritonitis from a population of 1930 patients over a period of 1 year. Moreover, the predominant causative organisms were almost identical to those in our study and other case series:[2,3] *E. coli*, *Klebsiella* species, *Enterobacter* species, and *Serratia* species, in descending order of frequency. The poorer outcomes associated with NPGN peritonitis and the identities of recovered organisms suggest the presence of underlying bowel pathology in a large proportion of affected patients. In keeping with this possibility, we observed that NPGN peritonitis was frequently polymicrobial (25% of cases) and was more common with increasing age.

When a single NPGN organism is identified by microscopy or culture in patients with PD-associated peritonitis, the ISPD guidelines recommend antibiotic therapy with a single agent based on sensitivities, safety, and convenience for a period of 3 weeks, regardless of whether or not the catheter is removed.[9] However, antibiotic treatment duration was not related to likelihood of cure in the present study. Moreover, the cure rate achieved with a median treatment period of 2 weeks in our study was comparable to that achieved in the studies by Bunke *et al.*[7] (mean treatment <2 weeks) and Szeto *et al.*[3] (treatment for 14–21 days). Based on the results of our study, reasonable cure rates can be achieved for single-organism NPGN peritonitis with single antimicrobial agents (most commonly aminoglycoside or quinolone) based on sensitivities for a period of 2 weeks.

Szeto *et al.*[3] further reported that recent antibiotic therapy was associated with marginally lower complete cure rates (49.3 vs 62.8%), although this was not found in our study. These results may be potentially explained by the relatively liberal prescription of antibiotics in the primary care setting in Hong Kong, as noted by Szeto *et al.*,[3] with the consequent development of antimicrobial resistance. In contrast, the main determinant of poorer peritonitis outcomes in the current study was recovery of multiple organisms, possibly reflecting the presence of underlying significant bowel pathology.[9] While early reports described polymicrobial peritonitis resulting from complications of catheter placement or bowel perforation,[12] later reports found polymicrobial peritonitis to be associated with a low incidence of catastrophic surgical pathology (2.8–9%).[13–17] In the present study, underlying bowel perforation requiring surgical intervention was reported in only a small proportion (1.1%) of NPGN peritonitis episodes. Surgical bowel pathology was significantly more common in NPGN peritonitis than in other forms of peritonitis and was significantly more common in polymicrobial than in

single-organism NPGN peritonitis (2.4 vs 0.6%, $P<0.05$, OR 3.77, 95% CI 1.004–14.2). However, the high proportion of polymicrobial NPGN peritonitis in our study and in that of Szeto *et al.*[17] suggests that the bowel may still be a common source. In cases of isolation of multiple enteric organisms, the ISPD guidelines recommend surgical evaluation, consideration of catheter removal, and treatment with metronidazole in combination with ampicillin and ceftazidime or an aminoglycoside. These recommendations are supported by the findings in our study, whereby polymicrobial peritonitis involving at least one NPGN organism was associated with greatly increased risks of catheter removal (50%), permanent hemodialysis transfer (43%), and death (6%). Our results suggest that polymicrobial NPGN peritonitis often warrants multiple antimicrobial agents and surgical evaluation.

In cases of refractory NPGN peritonitis, the ISPD guidelines recommend removal of the catheter within 5 days to protect the peritoneal membrane for future use.[9] However, removal of the catheter within the first 5 days of peritonitis onset as opposed to later did not significantly affect the probabilities of either permanent hemodialysis transfer or death in our study, regardless of whether single-organism or polymicrobial peritonitis episodes were considered. This finding was not likely to result from lack of statistical power, as the number of catheters removed during the study period ($n=793$) was large.

Although severe peritonitis has been identified in some reports as a risk factor for encapsulating peritoneal sclerosis (EPS),[18–20] no EPS cases were reported following NPGN peritonitis episodes in the present study. These results are in keeping with a recently published ANZDATA Registry study, which found that EPS was predicted by age and PD duration, but not by peritonitis rate or type.[21]

The strengths of this study included its very large sample size and inclusiveness. We included all patients receiving PD in Australia across 66 centers during the study period, such that a variety of centers with varying approaches to the treatment of peritonitis were included. This greatly enhanced the external validity of our findings. These strengths should be balanced against the study's limitations, which included limited depth of data collection. ANZDATA does not collect important information, such as the 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, antimicrobial susceptibilities of recovered organisms, antibiotic dosages, or routes of antibiotic administration. Even though we adjusted for a large number of patient characteristics, the possibility of residual confounding could not be excluded. 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, NPGN peritonitis is a frequent, serious complication of PD, which is associated with significant risks of hospitalization, catheter removal, permanent hemodialysis transfer, and death. Cure with antibiotics alone is achievable in only 60% of cases and is much less likely when multiple organisms are isolated.

MATERIALS 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 began 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), BMI, late referral (defined as commencement of dialysis within 3 months of referral to a nephrologists), microbiology of peritonitis episodes (up to three organisms for polymicrobial episodes), and the initial and subsequent antibiotic treatment regimens. Diagnosis of peritonitis was made based on a PD effluent white cell count $>100/\mu l$, with $>50\%$ polymorphonuclear leukocytes. In cases of polymicrobial peritonitis, NPGN peritonitis was recorded if an NPGN species was at least one of the isolated organisms. Center 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 over the study period), small–medium (11–38 patients), medium–large (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 hemodialysis, 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 was used) for peritonitis due to the same organism. A relapse was not counted as a separate episode of peritonitis. 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 was 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

Results were expressed as frequencies and percentages for categorical variables, mean ± s.d. for continuous variables, and median and interquartile range for non-parametric data. Differences between two groups of patients were analyzed by χ^2 test for categorical data, unpaired *t*-test for continuous parametric data, and Mann–Whitney test for continuous non-parametric data. The independent predictors of NPGN peritonitis were determined by multivariate, multilevel mixed-effects Poisson regression analysis. In order to account for the structure of the data, this multilevel hierarchical model was created with a random effect for state of residence, treating unit, and individual patient.[22] Predictors of peritonitis outcomes were determined by multivariate, multilevel mixed-effects logistic regression using stepwise backward elimination. First-order interaction terms between the significant covariates were examined for all analyses. Data were analyzed using the SPSS software package

for Windows release 12.0 (SPSS Inc., North Sydney, New South Wales, Australia) and Stata/s.e. 10.0 (College Station, TX, USA). P values <0.05 were considered statistically significant.

DISCLOSURE

DWJ is a consultant for Baxter Healthcare and has previously received research funds from this company. He has also received speakers' honoraria and research grants from Fresenius Medical Care. KMB is a consultant for Baxter Healthcare. FGB is a consultant for Baxter and Fresenius and has received travel grants from Amgen and Roche. SPM has received speaking honoraria from AMGEN Australia, Fresenius Australia, and Solvay Pharmaceuticals and travel grants from AMGEN Australia, Genzyme Australi, and Jansen-Cilag. The remaining authors declared no competing interests.

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