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# Coagulase-negative staphylococcal peritonitis in Australian peritoneal dialysis patients: predictors, treatment and outcomes in 936 cases

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## Abstract

**Background.** Coagulase-negative staphylococcal (CNS) peritonitis is the most common cause of peritoneal dialysis (PD)-associated peritonitis. Previous reports of this important condition have been sparse and generally limited to single-centre studies.

**Methods.** The frequency, predictors, treatment and clinical outcomes of CNS peritonitis were examined by multivariate logistic regression and multilevel Poisson regression in all adult PD patients in Australia between 2003 and 2006.

**Results.** A total of 936 episodes of CNS peritonitis (constituting 26% of all peritonitis episodes) occurred in 620 individuals. The observed rate of CNS peritonitis was 0.16 episodes per patient-year. Lower rates of CNS peritonitis were independently predicted by Asian racial origin (adjusted odds ratio [OR], 0.52; 95% CI, 0.35–0.79), renovascular nephrosclerosis (OR, 0.40; 95% CI, 0.18–0.86), early referral to a renal unit prior to dialysis commencement (OR, 0.38; 95% CI, 0.19–0.79) and treatment with automated PD at any time during the PD career (OR, 0.79; 95% CI, 0.66–0.96). The majority of CNS peritonitis episodes were initially treated with intraperitoneal vancomycin or cephazolin in combination with gentamicin. This regimen was changed in 533 (57%) individuals after a median period of 3 days, most commonly to vancomycin monotherapy. The median total antibiotic course duration was 14 days. Compared with other forms of peritonitis, CNS episodes were significantly more likely to be cured by antibiotics alone (76 *vs* 64%, $P < 0.001$) and less likely to be complicated by hospitalization (61 *vs* 73%, $P < 0.001$), catheter removal (10 *vs* 26%, $P < 0.001$), temporary haemodialysis (2 *vs* 5%, $P < 0.001$), permanent haemodialysis transfer (9 *vs* 21%, $P < 0.001$) and death (1.0 *vs* 2.7%, $P = 0.002$). CNS peritonitis was also associated with a shorter duration of hospitalization, a longer time to catheter removal and a shorter duration of temporary haemodialysis. Catheter removal and permanent haemodialysis transfer were independently predicted by polymicrobial peritonitis and initial empiric administration of vancomycin (compared with cephalosporins). CNS peritonitis was associated with a higher relapse rate (17 *vs* 13%, $P = 0.003$) and relapsed CNS peritonitis was associated with a higher catheter removal rate (22 *vs* 7%, $P < 0.001$). Repeat peritonitis occurred in 194 (31%) individuals and the highest risk was in the second month after completion of antibiotic treatment for CNS peritonitis (OR, 1.87; 95% CI, 1.39–2.51 compared with >2 months).

**Conclusions.** CNS peritonitis is a common complication with a relatively benign outcome compared with other forms of PD-associated peritonitis. Relapsed and repeat peritonitis are relatively common and are associated with worse outcomes.

**Keywords:** antibiotics; microbiology; outcomes; peritoneal dialysis; peritonitis

## Introduction

Coagulase-negative staphylococci (CNS) are isolated in 11.4–39.9% of cases of culture-positive peritoneal dialysis (PD)-related peritonitis, representing the most common cause of PD-related peritonitis [1–6]. Rates of CNS-related peritonitis declined significantly in the early 1990s following the introduction of the 'Y'-set and double-bag connection systems [3–5,7,8]. However, subsequent rates of CNS-related PD peritonitis have remained static.

The ISPD guidelines describe CNS-related PD peritonitis as a generally mild form of peritonitis that often responds well to antibiotic therapy [9]. The committee recommends 2 weeks of antibiotic therapy and a review of patient technique, while in cases of relapsed peritonitis, catheter colonization with a biofilm should be suspected and treated by catheter removal [9]. However, reports of the predictors, clinical course, treatment and outcomes of

CNS peritonitis remain unclear because most available studies are based on older, small clinical studies involving single centres (often where PD expertise is concentrated) with limited depth of data collection and/or lack of a comparison group [1,2,6]. To date, there has not been a comprehensive, multicentre examination of CNS peritonitis risk factors and outcomes.

The aim of the current study was to examine the frequency, predictors, treatment and clinical outcomes of CNS peritonitis in all Australian PD patients, as recorded in the ANZDATA registry.

## Materials and methods

### *Study population*

This prospective observational study was planned at the commencement of the Australian Peritonitis Registry on 1 October 2003 when the ANZDATA Registry started collecting detailed peritonitis data. Previous analyses have already been published for PD peritonitis due to *Staphylococcus aureus* [10], streptococcus [11], enterococcus [12], corynebacterium [13], pseudomonas [14], fungus [15], polymicrobial organisms [16] and culture-negative infection [17]. The investigation included all Australian adult patients from the ANZDATA Registry who were receiving PD between 1 October 2003 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 nephrologists), PD modality [CAPD only *vs* automated PD (APD) ever], microbiology of peritonitis episodes (up to three organisms for polymicrobial episodes), initial and subsequent antibiotic treatment regimens and duration of antimicrobial course (calculated as the number of days elapsed between the first and last dose of antimicrobial agent). CNS peritonitis was defined as clinical features of peritonitis (abdominal pain or cloudy dialysate), dialysate leucocytosis (white blood cell count >100/μL with >50% neutrophils) and dialysate culture yielding CNS. In cases of polymicrobial peritonitis, CNS peritonitis was recorded if CNS 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), 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 haemodialysis and patient death. Peritonitis relapse was defined as a recurrence of CNS peritonitis due to the same organism occurring within 4 weeks of the last antibiotic dose (or within 5 weeks if intermittent vancomycin was used) for peritonitis. Repeat peritonitis was defined as an episode of CNS 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. Peritonitis-related death was recorded if the patient's death was directly attributable to peritonitis in the clinical opinion of the treating nephrologist. 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.

### *Statistical analysis*

Results were expressed as frequencies and percentages for categorical variables, mean ± standard deviation for continuous variables and median and interquartile range (IQR) for non-parametric data. Differences between the two groups of patients were analysed by chi-square test for categorical data, unpaired *t*-test for continuous parametric data and Mann–Whitney test for continuous non-parametric data. The independent predictors of CNS 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 [18]. 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 9.2 (College Station, TX). P-values <0.05 were considered statistically significant.

## 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. In this group, 3594 episodes of peritonitis occurred in 1984 (42%) patients and 936 episodes of CNS peritonitis occurred in 361 individuals. CNS peritonitis accounted for 26% of all peritonitis episodes in 18% of all patients experiencing peritonitis. The rates of all peritonitis and CNS peritonitis were 0.60 and 0.16 episodes per patient-year of treatment. The organisms isolated in cases of CNS peritonitis included *Staphylococcus epidermidis* (539 or 58%), CNS other (214 or 23%) and CNS unknown (207 or 22%). Two different CNS species were isolated in 24 (3%) episodes. Additional non-CNS organisms were isolated in 84 (10%) episodes of CNS peritonitis, including *S. aureus* ($n = 7$), streptococci ($n = 15$), enterococci ($n = 10$), corynebacteria ($n = 3$), other Gram-positive organisms ($n = 9$), pseudomonas ($n = 5$), acinetobacter ($n = 5$), *E. coli* ($n = 4$), *Klebsiella* ($n = 3$), enterobacter ($n = 3$), proteus ($n = 1$), neisseria ($n = 1$), other Gram-negative organisms ($n = 10$) and fungi ($n = 8$).

### *Predictors of CNS peritonitis*

The characteristics of patients who experienced CNS or non-CNS peritonitis are shown in Table 1. On univariate analysis, patients who experienced CNS peritonitis during the study period were more likely to be older, have a lower eGFR at dialysis commencement, have diabetes mellitus, have a low or low average baseline peritoneal transport status, spend a smaller proportion of their PD career receiving APD *vs* CAPD and were treated at a larger-sized PD centre than patients who did not experience CNS peritonitis. There was also a trend for males to be more likely to experience CNS peritonitis.

On multivariate multilevel mixed-effects Poisson regression analysis of all peritonitis episodes, lower rates of CNS peritonitis were significantly and independently predicted by Asian racial origin (adjusted odds ratio [OR], 0.52; 95% CI, 0.35–0.79), renovascular nephrosclerosis (OR, 0.40; 95% CI, 0.18–0.86), early referral to a renal unit prior to dialysis commencement (OR, 0.38; 95% CI, 0.19–0.79) and treatment with APD at any time during the PD career (OR, 0.79; 95% CI, 0.66–0.96). The development of CNS peritonitis was not associated with age, gender, BMI, smoking status, chronic lung disease, coronary artery disease, peripheral vascular disease, cerebrovascular disease, diabetes mellitus, eGFR at dialysis commencement, peritoneal transport status or centre size.

**Table 1.** Characteristics of all Australian PD patients who did or did not experience at least one CNS peritonitis episode during the period 2003–06

| Characteristic | CNS peritonitis ($n$ = 620) | No CNS peritonitis ($n$ = 4055) | P-value |
|---|---|---|---|
| Age (years) | 63.0 ± 15.9 | 61.3 ± 16.8 | 0.02 |
| Women, $n$ (%) | 260 (42) | 1866 (46) | 0.06 |
| Racial origin, $n$ (%) | | | 0.7 |
| Caucasian | 478 (77) | 3103 (77) | |
| ATSI | 53 (9) | 308 (8) | |
| MPI | 14 (2) | 93 (2) | |
| Asian | 50 (8) | 391 (10) | |
| Other | 25 (4) | 160 (4) | |
| BMI (kg/m$^2$) | 26.0 ± 5.2 | 25.9 ± 6.5 | 0.5 |
| eGFR at dialysis start (mL/min/1.73 m$^2$) | 6.8 ± 3.4 | 7.2 ± 4.6 | 0.04 |
| Late referral, $n$ (%) | 161 (26) | 950 (23) | 0.4 |
| ESRF cause, $n$ (%) | | | 0.2 |
| Chronic glomerulonephritis | 163 (26) | 1160 (29) | |
| Diabetic nephropathy | 193 (31) | 1126 (28) | |
| Renovascular disease | 95 (15) | 544 (13) | |
| Polycystic kidneys | 37 (6) | 219 (5) | |
| Reflux nephropathy | 22 (4) | 175 (4) | |
| Other | 79 (13) | 566 (14) | |
| Unknown | 31 (5) | 265 (7) | |
| Smoker, $n$ (%) | | | 0.13 |
| Current | 78 (13) | 479 (12) | |
| Former | 249 (40) | 1485 (37) | |
| Never | 293 (47) | 2091 (52) | |
| Chronic lung disease, $n$ (%) | 79 (13) | 520 (13) | 1.0 |
| Coronary artery disease, $n$ (%) | 228 (37) | 1439 (35) | 0.5 |
| Peripheral vascular disease, $n$ (%) | 140 (23) | 906 (22) | 0.9 |
| Cerebrovascular disease, $n$ (%) | 81 (13) | 527 (13) | 1.0 |
| Diabetes mellitus, $n$ (%) | 263 (42) | 1475 (36) | 0.004 |
| Proportion of PD career spent on APD, % | 0 [0–95] | 6 [0–100] | 0.03 |
| Peritoneal transport status, $n$ (%) | | | <0.001 |
| High | 64 (10) | 407 (10) | |
| High average | 230 (37) | 1481 (37) | |
| Low average | 173 (28) | 905 (22) | |
| Low | 34 (5) | 164 (4) | |
| Unknown/not specified | 119 (19) | 1098 (27) | |
| Centre size (no. of PD patients), $n$ (%) | | | 0.005 |
| Small (≤10) | 5 (0.8) | 50 (1.2) | |
| Small–medium (11–38) | 31 (5) | 290 (7) | |
| Medium–large (39–98) | 113 (18) | 915 (23) | |
| Large (≥99) | 471 (76) | 2800 (69) | |

ATSI, Aboriginal and Torres Strait Islander; MPI, Maori and Pacific Islander.

**Table 2.** Antimicrobial agents prescribed in the initial, second and third antibiotic regimens for CNS peritonitis episodes in Australian PD patients 2003–06

| Antibiotic | CNS peritonitis ($n$ = 936 episodes), $n$ (%) | | |
|---|---|---|---|
| | First regimen ($n$ = 936) | Second regimen ($n$ = 533) | Third regimen ($n$ = 95) |
| Cephazolin | 373 (40) | 52 (10) | 1 (1) |
| Vancomycin | 483 (52) | 377 (71) | 65 (68) |
| Gentamicin | 609 (65) | 45 (8) | 5 (5) |
| Ciprofloxacin | 53 (6) | 13 (2) | 6 (6) |
| Cefoxitin | 39 (4) | 3 (1) | 0 (0) |
| Ceftazidime | 94 (10) | 7 (1) | 2 (2) |
| Ceftriaxone | 23 (2) | 5 (1) | 1 (1) |
| Cephalothin | 59 (6) | 16 (3) | 1 (1) |
| Cephalexin | 2 (0.2) | 16 (3) | 8 (8) |
| Other cephalosporin | 14 (1) | 6 (1) | 2 (2) |
| Flucloxacillin/dicloxacillin/cloxacillin | 4 (0.4) | 9 (9) | 4 (4) |
| Amoxycillin | 2 (0.2) | 1 (0.2) | 1 (1) |
| Amoxycillin ± clavulanate | 22 (2) | 6 (1) | 3 (3) |
| Metronidazole | 2 (0.2) | 5 (1) | 1 (1) |
| Other[a] | 33 (4) | 19 (4) | 15 (16) |

Results represent the number of episodes treated with antibiotic (% of total treated with 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.

[a]Other includes amikacin, amphotericin B, aztreonam, clindamycin, erythromycin, fluconazole, imipenem, rifampicin, sulphamethoxazole/trimethoprim, ticarcillin, teicoplanin, tobramycin and unknown.

### *Treatment of CNS peritonitis*

The majority of patients with CNS peritonitis were treated with either intraperitoneal vancomycin or cephazolin in combination with gentamicin (Table 2). The initial antibiotic regimen was changed in 533 (57%) CNS peritonitis episodes after a median period of 3 days, with the predominant change being conversion to vancomycin monotherapy. Oral antibiotics were used at some stage in 78 (8%) patients, with the most common choice being cephalexin followed by amoxycillin with clavulanic acid and an isoxazolyl penicillin (typically flucloxacillin). Overall, the median total antibiotic course duration for CNS peritonitis was 14 days.

Although the ANZDATA Registry does not collect information about antimicrobial susceptibilities of organisms isolated from PD patients with peritonitis, the methicillin sensitivities of 627 (67%) CNS isolates from PD fluid were subsequently obtained separately from selected microbiology laboratories servicing the bulk of PD units in Australia during the period 2003–06. These are presented in Table 3 and consistently demonstrated that the majority (68%) of organisms were methicillin resistant.

In terms of adjunctive therapy, Tenckhoff catheter instillation with either urokinase or streptokinase was performed more commonly in CNS than non-CNS peritonitis (1.4 *vs* 0.6%, respectively, P = 0.03). Instillation of streptokinase or urokinase was significantly more common in the setting of relapsed CNS peritonitis (5 *vs* 0.6%, P < 0.001). There were no significant differences between the two groups with respect to the utilization of other adjunctive therapies, including rifampicin (0.5 *vs* 0.5%, P = 0.9), nystatin anti-fungal chemoprophylaxis (7 *vs* 7%, P = 0.4) or heparin administration to dialysate (21 *vs* 21%, P = 0.9).

### *Outcomes of CNS peritonitis*

Compared with non-CNS peritonitis, CNS peritonitis episodes were significantly more likely to be cured by antibiotics alone (76 *vs* 64%, P < 0.001) and less likely to be complicated by hospitalization (61 *vs* 73%, P < 0.001), catheter removal (10 *vs* 26%, P < 0.001), temporary haemodialysis (2 *vs* 5%, P < 0.001), permanent haemodialysis transfer (9 *vs* 21%, P < 0.001) or death (1.0 *vs* 2.7%, P = 0.002) (Table 4). CNS peritonitis was also associated with a shorter duration of hospitalization, a longer

time to catheter removal and a shorter duration of temporary haemodialysis. There was also a trend to a longer time to peritonitis-associated death. Using multivariate logistic regression, isolation of CNS from dialysate culture during a peritonitis episode was a significant, independent predictor of peritonitis cure with antibiotics alone (OR, 1.78; 95% CI, 1.49–2.13).

CNS peritonitis was associated with a significantly higher risk of relapse (17 *vs* 13%, P = 0.003), and patients who experienced a relapse of CNS peritonitis were significantly more likely to have their catheters removed than patients with CNS peritonitis who did not experience a relapse (22 *vs* 7%, P < 0.001; OR, 3.47; 95% CI, 2.18–5.52). In patients who did not undergo catheter removal, CNS peritonitis was still associated with a higher risk of relapse (15 *vs* 11%, P = 0.008).

With respect to repeat peritonitis, 426 (69%) patients experienced 1 episode, 124 (20%) experienced 2 episodes, 43 (7%) experienced 3 episodes, 18 (3%) experienced 4 episodes, 1 (0.2%) experienced 5 episodes, 4 (0.6%) experienced 6 episodes, 2 (0.3%) experienced 7 episodes, 1 (0.2%) experienced 8 episodes and 1 (0.2%) experienced 10 episodes. The highest risk of repeat peritonitis was in the second month after the completion of antibiotic treatment for CNS peritonitis (OR, 1.87; 95% CI, 1.39–2.51 compared with >2 months). The median [IQR] interval between a previous episode of peritonitis and subsequent peritonitis was significantly shorter for CNS peritonitis (65 [37–174] days) than for non-CNS peritonitis (89 [37–204] days, P = 0.0.05).

Hospitalization of patients with CNS peritonitis was significantly and independently predicted by younger age (OR, 0.986; 95% CI, 0.975–0.997), female gender (OR, 1.70; 95% CI, 1.24–2.33), Asian racial origin (OR, 0.51; 95% CI, 0.29–0.90), Aboriginal and Torres Strait Islander racial origin (OR, 0.47; 95% CI, 0.29–0.77), eGFR (OR, 1.07; 95% CI, 1.02–1.13), coronary artery disease (OR, 1.58; 95% CI, 1.10–2.25), use of an agent other than vancomycin or cephalosporin in the initial empiric antibiotic regimen (OR, 2.31; 95% CI, 1.33–4.01) and polymicrobial peritonitis (OR, 2.79; 95% CI, 1.60–4.85).

Catheter removal was significantly more likely with polymicrobial peritonitis (OR, 4.62; 95% CI, 2.60–8.22) and was less likely with the use of cephalosporins in the initial empiric antibiotic regimen (OR, 0.41; 95% CI, 0.23–0.72) compared with vancomycin therapy. The risk of permanent haemodialysis was similarly predicted by polymicrobial peritonitis (OR, 4.96; 95% CI, 2.73–8.99) and cephalosporin therapy (OR, 0.46; 95% CI, 0.26–0.83). No independent predictors of peritonitis-associated death were identified, although the number of events was low.

### *Effect of timing of catheter removal in CNS peritonitis*

Tenckhoff catheter removal occurred in 91 (10%) of the 936 episodes of CNS peritonitis after a median period of 11 days. When outcomes were compared between early (within 7 days) and late (after 7 days) catheter removal, there were no significant differences observed with respect to permanent haemodialysis transfer (88 *vs* 77%, respectively, P = 0.2) or death (3 *vs* 2%, P = 0.7).

## Discussion

The present study represents the most comprehensive examination to date of the frequency, predictors, treatment and clinical outcomes of PD-associated CNS peritonitis. CNS peritonitis was found to account for 26% of all PD-related peritonitis episodes, was more common in patients who were referred late to a renal unit for dialysis and was less common in Asian patients, those with renovascular nephrosclerosis and those who received APD therapy at any time during their PD career. The higher rate of CNS peritonitis in late referred patients may represent poorer quality of pre-dialysis care and possibly poorer PD training. Alternatively, adherence to proper PD technique may more often be suboptimal in late referred patients, leading to an increased possibility of peritoneal contamination with CNS. The lower risks of CNS peritonitis in Asian patients and those with renovascular nephrosclerosis are unexplained, although Asian patients do have overall lower peritonitis rates and higher technique survival compared with non-Asian PD patients in Australia. This may reflect better adherence to proper PD technique or innate resistance to PD-associated peritonitis following spike contamination. The lower rates of CNS peritonitis in patients receiving APD therapy compared with those solely treated with CAPD may reflect fewer connections with APD and, therefore, reduced risk of contamination with skin organisms, such as CNS.

Interestingly, the largest centres were found on univariate analysis to be associated with a significantly increased risk of CNS peritonitis. While we were able to adjust for such centre effects in the multilevel hierarchical modelling, the precise reason for this association is uncertain. One possible explanation may relate to lower PD nurse to patient ratios in larger centres, which may in turn adversely impact on patient training and PD exchange technique. Studies examining ideal nurse to patient ratios have not been performed, but there is consensus that overburdening of nurses adversely impacts on patient training quality [9,19]. This important aspect of patient care requires further formal evaluation.

Our study demonstrated largely favourable outcomes for CNS PD-related peritonitis, which were in keeping with those reported in other series [1,2,6]. Szeto *et al*. [6] reported on the outcomes of 232 episodes of CNS PD-related peritonitis in 155 patients over an 11-year period. The observed rate of CNS-related peritonitis in this series was 11.4% and was markedly lower than that reported in the current study and other series [1–5], perhaps reflecting a different microbiological spectrum unique to that centre/region or a lower propensity for CNS peritonitis in Asian patients. The authors reported a comparable cure rate by antibiotics alone of 71.1%, a markedly higher mortality rate of 2.6% and significantly lower rates of PD catheter removal (2.2%) and permanent haemodialysis transfer (0.6%). Unfortunately, no comparison was made with other causes of PD-related peritonitis in the same population, making it difficult to interpret the relative significance of these outcomes compared with other causes of PD-related peritonitis. With regards to the mortality rate, the authors commented that, in their opinion, only one of the six reported deaths in their series could be directly attributed

**Table 3.** Methicillin sensitivities of CNS isolated from PD fluid in selected microbiology laboratories servicing the bulk of PD units in Australia during the period 2003–06

| Australian State | Number of CNS PD isolates | Number tested for methicillin resistance | % methicillin resistant |
|---|---|---|---|
| Queensland | 219 | 202 | 69 |
| Victoria | 57 | 42 | 62 |
| South Australia | 114 | 114 | 62 |
| New South Wales | 117 | 117 | 66 |
| Western Australia | 120 | 120 | 77 |
| Totals | 627 | 595 | 68 |

These organisms accounted for 67% of all CNS peritonitis episodes during the study period.

to peritonitis per se, equating to a mortality rate of 0.6%. Whether such an assertion can be made with confidence is unclear, especially since the other five deaths were related to either infectious or cardiovascular causes. The low catheter removal and haemodialysis transfer rates were also out of keeping with those reported elsewhere [1,2]. This finding probably reflects the predominant (>80%) utilization of PD as a renal replacement therapy in Hong Kong whereby haemodialysis transfer occurs as a last resort such that patients are 'switched to haemodialysis only when they have ultrafiltration failure or peritoneal sclerosis'.

Bunke *et al*. [1] examined 530 episodes of PD-related peritonitis caused by a single organism in a cohort of 1930 patients over 1 year and noted that 242 (46%) of these episodes were caused by CNS. In keeping with the favourable outcomes reported here, the authors found that CNS-related peritonitis had relatively high rates of resolution (83.8%) and low rates of catheter removal (4.6%), hospitalization (17.9%), transfer to haemodialysis (1.3%) and death (0.8%) compared with non-pseudomonal Gram-negative and *S. aureus* PD-related peritonitis episodes.

Finally, Mujais [2] reported on the outcomes of single-organism PD-related peritonitis in a cohort of 9655 US and Canadian patients over a 6-year period. Unfortunately, outcome data were only available for 37.2% of all peritonitis episodes in the US cohort and 52.8% of episodes in the Canadian cohort. The completeness of the data source for CNS peritonitis outcomes was not recorded in the report nor was the definition of 'resolution'. Despite these methodological issues, the outcomes of CNS PD-related peritonitis were reported as a resolution rate of 92.6% in US patients and 92.1% in Canadian patients, a catheter removal rate of 6.7% in US patients and 6.5% in Canadian patients and a mortality rate of 0.7% in US patients and 1.4% in Canadian patients. The author commented that 'among Gram-positive organisms, coagulase-negative infections had the best outcomes'; however, no formal statistical analysis was included to substantiate this conclusion and no comparison was performed with Gram-negative or culture-negative PD-related peritonitis groups.

Our study demonstrates that CNS peritonitis is associated with a significantly higher risk of relapse (17 *vs* 13%, P = 0.003) compared with other causes of PD-related peritonitis. This finding may represent competing risks since CNS peritonitis episodes are more likely to be associated with the catheter remaining *in situ* (thereby exposing patients to the risk of relapse) than non-CNS peritonitis. Alternatively, it may represent a true risk related to CNS since CNS peritonitis was associated with a higher risk of relapse even in patients who did not undergo

**Table 4.** Treatment characteristics and clinical outcomes of CNS and non-CNS PD-associated peritonitis in Australia 2003–06

| Outcome | CNS peritonitis ($n$ = 936 episodes) | Culture-positive peritonitis ($n$ = 2658 episodes) | P-value |
|---|---|---|---|
| Treatment | | | |
| Change to second antibiotic regimen | 533 (57) | 1477 (56) | 0.5 |
| Time to second antibiotic regimen | 3 [2–5] | 3 [1–5] | 0.9 |
| Change to third antibiotic regimen | 95 (10) | 402 (15) | <0.001 |
| Time to third antibiotic regimen | 6 [4–9] | 6 [4–10] | 0.6 |
| Total antibiotic treatment duration | 14 [8–18] | 14 [8–20] | 0.12 |
| Peritonitis relapse | 158 (17) | 344 (13) | 0.003 |
| Hospitalization | | | |
| Number (%) | 569 (61) | 1935 (73) | <0.001 |
| Duration | 5 [3–9] | 6 [3–13] | <0.001 |
| Catheter removal | | | |
| Number (%) | 91 (10) | 684 (26) | <0.001 |
| Time to occurrence | 11 [4–34] | 6 [3–11.25] | 0.001 |
| Temporary haemodialysis | | | |
| Number (%) | 18 (2) | 134 (5) | <0.001 |
| Time to occurrence | 3.5 [0.75–26.75] | 6 [3–11] | 0.6 |
| Duration | 60.5 [11.25–80] | 69 [27–105] | 0.2 |
| Permanent haemodialysis | | | |
| Number (%) | 81 (9) | 554 (1219) | <0.001 |
| Time to occurrence | 9 [5–26] | 7 [4–12] | 0.009 |
| Death | | | |
| Number (%) | 9 (1.0) | 73 (2.7) | 0.002 |
| Time to death | 22 [6–55] | 10 [2.5–21.5] | 0.07 |
| Uncomplicated (no relapse, catheter removal or death) | 716 (76) | 1714 (64) | <0.001 |

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

catheter removal. The observation of a higher risk of relapse in CNS peritonitis is supported by the finding that pathogenic strains of CNS are able to produce enzymes and polysaccharide slime (biofilm) that enhance their adherence to prosthetic surfaces [20]. Furthermore, a small series demonstrated that, in relapsing PD peritonitis caused by CNS, the biotype of the organism cultured from PD effluent was the same as that grown from culturing of the catheter [21]. Our analysis also found that, among patients experiencing a relapse of CNS peritonitis, catheter removal was significantly more likely than among patients with CNS peritonitis who did not experience a relapse (22 *vs* 7%, $P < 0.001$; OR, 3.47; 95% CI, 2.18–5.52). Once again, this is probably explained by the ability of CNS to produce biofilms and adhere to the catheter surface, necessitating catheter removal in some cases for cure—a practice advocated by the ISPD [9]. Alternatively, indication bias may explain the findings since it is possible that the ISPD recommendation of catheter removal in the setting of relapsed CNS peritonitis acted as a driver for catheter removal in patients with relapsed CNS peritonitis. In support of our findings, Szeto *et al*. [6] reported a significantly lower cure rate for relapsed and repeat CNS-related peritonitis in their cohort (54.4 *vs* 76.6%, $P = 0.002$), but did not specifically describe the risk of catheter removal with relapse of CNS-related PD peritonitis.

With regards to therapy-specific associated outcomes, the most striking findings were that catheter removal was significantly less likely with the use of cephalosporins compared with vancomycin therapy in the initial empiric antibiotic regimen (OR, 0.41; 95% CI, 0.23–0.72), as was the risk of permanent haemodialysis transfer (OR, 0.46; 95% CI, 0.26–0.83). It is unlikely that these findings represent inferiority of vancomycin, as previously published studies have demonstrated equivalence of cephalosporins and vancomycin in the treatment of CNS-related peritonitis [6,22]. Rather, these findings most likely represent non-random initial antibiotic choice and confounding by indication, with vancomycin being more likely to be prescribed in higher-risk situations (e.g. relapse/repeat peritonitis, previous recent hospitalization, etc.). Other potential explanations include the fact that vancomycin tends to be used in outpatient settings which may have indicated remote residence or too infrequent dosing and, therefore, poorer outcome.

Our findings support the assertion of the ISPD guidelines that CNS PD-related peritonitis is a generally mild form of peritonitis that responds well to antibiotics alone and that relapsed CNS PD-related peritonitis likely represents catheter colonization with a biofilm and often necessitates catheter removal for cure. In addition, the median duration of antibiotic therapy in our study was at least 14 days, in keeping with the ISPD guidelines. In cases in which vancomycin was used, it is likely that the duration of antibiotic therapy was appreciably longer than 14 days as vancomycin is known to exert antimicrobial activity for up to a week after administration.

The strengths of this study included its very large sample size and inclusiveness. We included all patients receiving PD in Australia during the study period, such that a variety of centres were included 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 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 (including the use of prophylactic mupirocin), laboratory values (such as C-reactive protein and dialysate white cell counts), severity of comorbidities, antimicrobial susceptibilities, 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. Furthermore, the reasons underpinning antibiotic choices, changes and treatment durations were not captured by ANZDATA, making it difficult to draw firm conclusions about the relationship between prescribed antibiotics and outcomes. The true prevalence of previous antibiotic use was likely underestimated as ANZDATA only recorded information about antibiotic prescription for peritonitis.

## Conclusion

In conclusion, our study represents the most comprehensive examination to date of the frequency, predictors, treatment and clinical outcomes of CNS PD-associated peritonitis and demonstrates that timely institution of antibiotic therapy produces clinical outcomes that are more favourable to those of other causes of culture-positive peritonitis. Nevertheless, CNS peritonitis is commonly complicated by relapse (17%) and repeat episodes (31%), which are associated with worse outcomes.

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## References


1. Bunke CM, Brier ME, Golper TA. Outcomes of single organism peritonitis in peritoneal dialysis: gram negatives *versus* gram positives in the Network 9 Peritonitis Study. *Kidney Int* 1997; 52: 524–529
2. Mujais S. Microbiology and outcomes of peritonitis in North America. *Kidney Int Suppl* 2006; S55–S62
3. 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: 1009–1013
4. Kim DK, Yoo TH, Ryu DR *et al*. Changes in causative organisms and their antimicrobial susceptibilities in CAPD peritonitis: a single center's experience over one decade. *Perit Dial Int* 2004; 24: 424–432
5. Brown F, Liu WJ, Kotsanas D, Korman TM, Atkins RC. A quarter of a century of adult peritoneal dialysis-related peritonitis at an Australian medical center. *Perit Dial Int* 2007; 27: 565–574
6. Szeto CC, Kwan BC, Chow KM *et al*. Coagulase negative staphylococcal peritonitis in peritoneal dialysis patients: review of 232 consecutive cases. *Clin J Am Soc Nephrol* 2008; 3: 91–97
7. Daly CD, Campbell MK, Macleod AM *et al*. Do the Y-set and double-bag systems reduce the incidence of CAPD peritonitis? A systematic review of randomized controlled trials. *Nephrol Dial Transplant* 2001; 16: 341–347
8. Strippoli GF, Tong A, Johnson D, Schena FP, Craig JC. Catheter-related interventions to prevent peritonitis in peritoneal dialysis: a systematic review of randomized, controlled trials. *J Am Soc Nephrol* 2004; 15: 2735–2746
9. Piraino B, Bailie GR, Bernardini J *et al*. Peritoneal dialysis-related infections recommendations: 2005 update. *Perit Dial Int* 2005; 25: 107–131
10. Govindarajulu S, Hawley C, McDonald SP *et al*. *Staphylococcus aureus* peritonitis in Australian peritoneal dialysis patients: predictors, treatment and outcomes in 503 cases. *Perit Dial Int* 2009; In press
11. O'Shea S, Hawley CM, McDonald SP *et al*. Streptococcal peritonitis in Australian peritoneal dialysis patients: predictors, treatment and outcomes in 287 cases. *BMC Nephrol* 2009; 10: 19
12. Edey M, Hawley C, McDonald SP *et al*. Enterococcal peritonitis in Australian peritoneal dialysis patients: predictors, treatment and outcomes in 116 cases. *Nephrol Dial Transplant* 2009; 25: 1272–1278
13. Barraclough K, Hawley CM, McDonald SP *et al*. Corynebacterium peritonitis in Australian peritoneal dialysis patients: predictors, treatment and outcomes in 82 cases. *Nephrol Dial Transplant* 2009; 24: 3834–3839
14. Siva B, Hawley CM, McDonald SP *et al*. Pseudomonas peritonitis in Australia: predictors, treatment, and outcomes in 191 cases. *Clin J Am Soc Nephrol* 2009; 4: 957–964
15. Miles R, Hawley CM, McDonald SP *et al*. Predictors and outcomes of fungal peritonitis in peritoneal dialysis patients. *Kidney Int* 2009; 76: 622–628
16. Barraclough K, Hawley CM, McDonald SP *et al*. Polymicrobial peritonitis in peritoneal dialysis patients in Australia: predictors, treatment, and outcomes. *Am J Kidney Dis* 2009; 55: 121–131
17. Fahim M, Hawley CM, McDonald SP *et al*. Culture-negative peritonitis in peritoneal dialysis patients in Australia: predictors, treatment and outcomes in 435 cases. *Am J Kidney Dis* 2009; 55: 690–697
18. Goldstein H. *Multilevel Statistical Models*. London: Hodder Arnold, 2003
19. Bender FH, Bernardini J, Piraino B. Prevention of infectious complications in peritoneal dialysis: best demonstrated practices. *Kidney Int Suppl* 2006; S44–S54
20. Spare MK, Tebbs SE, Lang S *et al*. Genotypic and phenotypic properties of coagulase-negative staphylococci causing dialysis catheter-related sepsis. *J Hosp Infect* 2003; 54: 272–278
21. Amato D, de JV, Miranda G *et al*. Staphylococcal peritonitis in continuous ambulatory peritoneal dialysis: colonization with identical strains at exit site, nose, and hands. *Am J Kidney Dis* 2001; 37: 43–48
22. Ariano RE, Franczuk C, Fine A, Harding GK, Zelenitsky SA. Challenging the current treatment paradigm for methicillin-resistant *Staphylococcus epidermidis* peritonitis in peritoneal dialysis patients. *Perit Dial Int* 2002; 22: 335–338


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