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Non-tuberculous mycobacterial PD peritonitis in Australia

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Abstract
Purpose Peritonitis can be a severe complication of peritoneal dialysis (PD) due to associated morbidity and mortality. Non-tuberculous mycobacteria (NTM) are a rare cause of PD peritonitis, with high rates of catheter removal and conversion to haemodialysis, and a reported mortality as high as 40 %. The incidence, culprit NTM species, and outcomes associated with PD peritonitis have not been described in many countries, including Australia.
Methods We examined the Australia and New Zealand Dialysis and Transplant Registry from 1 October 2003 to 31 December 2009 for all prevalent peritoneal dialysis patients. Patient characteristics, organisms, treatment and outcome for all NTM PD peritonitis episodes were obtained.
Results Twelve cases of NTM PD peritonitis were reported, including the first reports of infection due to *Mycobacteriumhassiacum* and *Mycobacterium neoaurum*. The incidence of NTM PD peritonitis was approximately 1 per 1000 PD patient-years. Recovery occurred in 11 patients, including 3 without removal of their Tenckhoff catheters. A range of antibiotics were utilised. One patient died of sclerosing peritonitis 5 months after diagnosis of PD peritonitis.
Conclusion Non-tuberculous mycobacteria PD peritonitis is a rare cause of peritonitis, and mortality may be lower than previously reported. Catheter removal occurred in the majority of patients, and adverse outcomes were not observed for those in whom it was retained.

Keywords Incidence · Mortality · *Mycobacterium* · Peritoneal dialysis · Peritonitis · Treatment

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Introduction

Peritoneal dialysis associated peritonitis (PD peritonitis) is a common cause of morbidity in patients receiving peritoneal dialysis (PD); 70 % of patients receiving PD in Australia and New Zealand will experience an episode of PD peritonitis within 3 years of commencing treatment [1]. Peritoneal dialysis peritonitis is associated with hospitalisation, risk of sepsis,

technique failure requiring conversion to haemodialysis and death. Approximately 25 % of technique failures are due to PD peritonitis [1]. Technique failure occurs in association with PD catheter removal secondary to persistent infection, or with fibrosis of the peritoneal membrane rendering it inadequate for dialysis.

Guidelines have been developed by the International Society of Peritoneal Dialysis (ISPD) to improve the management of PD peritonitis [2]. These guidelines recommend intraperitoneal gentamicin together with either cephazolin or cephalothin as first-line treatment for PD peritonitis. This is based on epidemiological studies reporting typical pathogens; however, it is also recommended that the guidelines are refined by individual units to consider locally relevant pathogens and resistance profiles [2].

Non-tuberculous mycobacteria (NTM) are considered a rare cause of PD peritonitis worldwide, including Australia, although the incidence has not been described in a population-based cohort. Non-tuberculous mycobacteria are classified as either rapid or slow growing, defined by their capacity to form colonies observable to the naked eye before or after 7 days of culture, respectively [3]. Even rapid growing NTM often require a minimum of 4 days to culture. Due to these qualities, the diagnosis and speciation of NTM is usually delayed. Non-tuberculous mycobacteria are incompletely sensitive to this first-line antibiotic therapy, and given the slow growth rate, many cases may initially be diagnosed as refractory culture-negative PD peritonitis, resulting in multiple antibiotic courses. Tenckhoff catheter removal is indicated for refractory PD peritonitis and may be considered for mycobacterial infections [2].

The low incidence of NTM infection has complicated efforts to examine their behaviour and response to treatments. Further, risk factors have not been clearly defined due to the few case series in the literature and inconsistent reporting of patient variables. We aim to examine the characteristics of NTM peritonitis in the Australian population reported in the Australian and New Zealand dialysis and transplant (ANZDATA) registry, as well as experience with treatment and outcomes.

Patients and methods

This study included all Australian dialysis and transplant registry (ANZDATA) patients over the age of 18 with an episode of PD peritonitis between 1 October 2003 and 31 December 2009. Patients were followed up until death or the most recent ANZDATA census (31st December 2009). Peritoneal dialysis peritonitis is diagnosed according to local criteria and, therapy decisions were determined by the treating site.

Detailed data for PD peritonitis organisms in Australian patients have been collected by ANZDATA since 1 October 2003. Pathogens are identified according to routine local hospital practice.

We retrospectively identified all cases of NTM PD peritonitis reported to ANZDATA. Deidentified data on demographics, native kidney disease, comorbid chronic disease (chronic lung disease, peripheral vascular disease, coronary artery disease, diabetes mellitus), duration of PD, mycobacterium isolated, treatment regimen, relapse episodes and PD catheter removal were obtained.

Demographics were reported as the median and interquartile range (IQR). Incidence rates were calculated against the annual ANZDATA reported prevalent PD cohort and exact Poisson confidence intervals calculated using Stata version 11 (StataCorp, College Station, Texas). The low frequency of events prevented formal analysis of the patient characteristics predicting the development of NTM peritonitis, which were therefore reported descriptively.

Results

Patient characteristics

Twelve episodes of PD peritonitis due to NTM were reported in 12 patients between October 2003 and December 2009. Patients had a median age of 62 years and were predominantly males (8/12), and all were white. The median duration of peritoneal dialysis prior to NTM peritonitis diagnosis was 1.5 years. The causes of end-stage renal failure were similar between the NTM peritonitis cohort and the greater ANZDATA cohort, with the most common causes of end-stage renal failure being diabetes ($n = 5$, 36 %) and glomerulonephritis ($n = 4$, 29 %) [1]. Five (36 %) patients had previously been diagnosed with an episode of PD peritonitis: One case due to *Enterococcus* occurred 11 days prior, and the others occurred at least 2–3 months previously of which three were culture negative. Baseline demographics and comorbid disease are listed in Table 1.

Table 1 Baseline demographics of patients with non-tuberculous mycobacterial peritonitis

Variable	Number
Male [*n* (%)]	8 (67)
Age (years; *median (IQR)*)	62 (15)
Duration of PD prior to infection *(years; median (IQR))*	1.5 (0.5, 2)
Body mass index *(kg/m^2; median (IQR))*	25.8 (22.4, 34.8)
Comorbidities [*n* (%)]	
Diabetes mellitus	5 (42)
Peripheral vascular disease	5 (42)
Coronary artery disease	5 (42)
Chronic lung disease	2 (17)
Cerebrovascular disease	1 (8)
Aetiology of renal failure [*n* (%)]	
Diabetic nephropathy	5 (42)
Glomerulonephritis	4 (33)
Lupus	2 (17)
Mesangiocapillary GN	1 (8)
Focal segmental glomerulosclerosis	1 (8)
Hypertension	1 (8)
Scleroderma	1 (8)
Obstructive uropathy	1 (8)

Table 2 Incidence of NTM peritonitis

Years	Incidence per 1000 PD patient-years (95 % CI)
2004	0.6 (0.01–3.1)
2005	1.1 (0.1–3.9)
2006	1.0 (0.1–3.5)
2007	1.4 (0.3–4.1)
2008	0.9 (0.1–3.2)
2009	0.9 (0.1–3.3)

The most common species causing NTM peritonitis were *M. abscessus*, *M. smegmatis* and *M. Chelonae,* although the single largest group was unspecified rapid growing NTM. The incidence of NTM peritonitis ranged between 1/1793 in 2004 to 3/2135 in 2009 or approximately 1/1000 PD patient-years during the study period (Table 2).

Treatment

The initial treatment was gentamicin and either vancomycin or cephazolin in 9 patients (75 %; Table 3). Second-line therapy was required in all, except one patient in whom successful treatment with ciprofloxacin and clarithromycin was reported to be first-line therapy and did not require removal of their Tenckhoff catheter (patient 4, Table 3; it is assumed that this patient had a milder clinical presentation so antibiotics were not administered immediately). A highly heterogeneous selection of antibiotics was used for second and third-line treatment (Table 3), presumably on the basis of microbiological isolates and local experience with such organisms; data were not available to confirm the rationale for such choices. Overall, 3 patients in our population were successfully treated without the removal of their Tenckhoff catheter, and none of these patients required conversion to haemodialysis at a median follow-up of 36 months. In all other cases, the Tenckhoff catheter was removed and the patient converted to haemodialysis. None of the patients who converted to haemodialysis recommenced PD at a later date.

One patient with *M. abscessus* PD peritonitis (patient 5, Table 3) died due to sclerosing peritonitis 5 months after diagnosis, despite the removal of the Tenckhoff catheter. As of 31 December 2009, 5 patients from the study population had died; in the remaining 4 patients, the cause of death was not attributed to NTM PD peritonitis. The median time to death was 2 years and 5 months.

Discussion

This study is the first to describe the incidence of NTM PD peritonitis in Australia and also in a population-based cohort. Non-tuberculous mycobacteria PD peritonitis is a rare cause of infective PD peritonitis in Australia, with an incidence of approximately 1/1000 PD patient-years and two new NTM species were identified as pathogens. A broad variety of specific antibiotic regimens were utilised, the Tenckhoff catheter was removed in 9 (75 %) of cases and only one death was temporally associated with the infection. No patient characteristics were clearly predictive of the development of NTM peritonitis. These patients did not obviously differ from the overall ANZDATA PD cohort with respect to demographic details, previous episodes of PD peritonitis or aetiology of kidney disease. The low incidence limited more detailed statistical examination of the demographics.

Table 3 NTM, treatment, and catheter survival

Organism	Patient identifier	Age, sex	Method of PD	1st line	2nd line	3rd line	PD catheter removal	Duration of follow-up (months)
M. hassiacum	1	63, M	CAPD	CEZ/GM	CEZ		Yes	29
Mycobacteria sp. Rapid Grower (unspecified)	2	46, F	CAPD	CEZ/GM	VAN	AM/Other	Yes	18
	3	62, M	CAPD	AM[a]	CXT		Yes	4
	4	74, M	CAPD	CPX/CLA[a]			No	36
M. abscessus	5	49, M	CAPD	CEZ/GM	GM	CEZ/Other	Yes	5
	6	40, F	APD	VAN/GM	FX	AM/CXT/Other	Yes	36
	7	65, M	APD	CLA[a]	VAN/TCC GM		Yes	15
M. chelonae	8	68, M	CAPD	CEZ/GM	TCC		Yes	9
	9	51, M	APD	VAN/GM	CLA		No	30
M. neoaurum	10	45, F	APD	VAN/GM	CPX/AM		No	53
M. smegmatis	11	61, M	APD	GM	VAN/GM	CPX/TMP-SMX/AS/MET	Yes	5
	12	62, F	CAPD	VAN/GM	AM/TMP-SMX		Yes	36

AM amikacin, *APD* automated peritoneal dialysis, *AS* ampicillin + sulbactam, *CAPD* continuous ambulatory peritoneal dialysis, *CEZ* cephazolin, *CLA* clarithromycin, *CPX* ciprofloxacin, *CXT* cefoxitin, *FX* flucloxacillin, *GM* gentamicin, *MET* metronidazole, *TCC* ticarcillin + clavulanic acid, *TMP-SMX* trimethoprim + sulfamethoxazole, *VAN* vancomycin

[a] Presume that non-routine antibiotics were given first line because the patient had a milder clinical presentation

Prior to this series, *Mycobacterium hassiacum* and *Mycobacterium neoaurum* had not been described as causes of NTM PD peritonitis. Although *M. neoaurum* is known to cause disease, particularly pulmonary and catheter-related sepsis in immunosuppressed patients [4, 5], it has not previously been reported as a cause of PD peritonitis. *Mycobacterium hassiacum* was first described in 1997 [6] and has not previously been reported as a cause of human disease. Previously reported cases of NTM peritonitis implicate *M. abscessus*, *M. fortuitum and M. chelonae* as the most common offending pathogens [7]. Only recently, *M. smegmatis* was first described as a cause of NTM peritonitis [8].

Mycobacterium fortuitum is considered one of the more common causes of NTM PD peritonitis [7, 9–11]; however, no cases due to this infection were reported in our population during this study period (although a case was subsequently noted [12]). The differences in NTM species in our series compared with others may represent geographical variability, local differences in sampling or analysis of PD effluent or variability in microbiological methods used to identify and speciate NTM. It is unclear whether the identity of the organisms described in our series was confirmed by genotyping which is considered the gold standard for identification of NTM. In 3 cases (patients 2, 3 and 4; Table 3), the isolate was imprecisely identified as an unspecified rapid growing NTM. However, a relationship between NTM species and prognosis in PD peritonitis has not been reported.

Although rare, this report suggests a relatively steady annual incidence of infection at a rate of approximately 1 per 1000 PD patient-years. This rate may be an over-or an under-estimate of the true rate. Isolation of a bacterium does not necessarily confirm causality and incorrectly attributing an NTM isolate as the cause of PD peritonitis would lead to an overestimate of the true incidence. In all these cases of PD peritonitis, we feel false attribution is less likely as NTM were the only bacteria isolated although the possibility cannot be excluded. Similarly, under reporting of NTM (or other organisms) resulting from inadequate microbiological methods cannot be

excluded. A recent publication suggested that a diagnosis of culture-negative PD peritonitis may reflect, in part, inadequate sample collection or methods used for bacterial culture [13]. Non-tuberculous mycobacteria are an important differential diagnosis of cases of apparent culture-negative peritonitis given the relatively prolonged time required for a positive culture. Improved awareness of NTM as an aetiology of PD peritonitis may lead to improvements in the use of bacterial culture and genotyping in patient management.

The first-line treatment of gentamicin and either vancomycin or cephazolin is common empiric antibiotic regimens utilised in Australian and New Zealand dialysis units, reflecting guidelines published by ISPD [2] and Caring for Australasians with Renal Impairment Guidelines [14]. We observed that a broad variety of second and third-line agents were utilised for the treatment of NTM PD peritonitis (this is not uncommon [7]) and may reflect the limited experience in treating this uncommon infection. Although antibiotic sensitivities can be performed on NTM, some debate exists regarding the clinical significance [15, 16].

A recent case series of NTM peritonitis from Asia (Singapore, $n = 10$) reported a mortality rate of 40 % at 3 months after diagnosis [10], considerably higher than 14.3 % reported in a systematic review ($n = 57$, but included data from the Singapore study) [7] or 8 % noted in our series. Further, our estimate is likely to be a conservative one given that this patient died 5 months after the diagnosis of NTM due to sclerosing peritonitis, a condition for which multiple causes is reported [17]. It is not possible to determine why outcomes differed between these studies, but in part it may reflect publication bias.

The Tenckhoff catheter was removed in 92.9 % of patients with NTM PD peritonitis in the systematic review [7]. In contrast, the catheter was removed in only 75 % of patients in our series, and adverse outcomes were not reported for those in whom it was retained. Unfortunately, indications for catheter removal are incompletely described, and our series did not clarify this clinical dilemma. The most common indication for catheter removal in the systematic review was refractory PD peritonitis [7], but this is an ISPD indication regardless of the culprit organism [2]. More research is required to identify indications specific to NTM PD peritonitis necessitating removal of the Tenckhoff catheter.

To our knowledge, this is the first population-based cohort study describing the incidence of NTM PD peritonitis. A strength of this methodology is the use of a database with near-universal coverage of the Australian dialysis population leading to an incidence rate calculation that is more likely to be a true reflection of the incidence than case series from individual units. Further, this comprehensive survey of a large dialysis population identified two species of NTM that have not previously been reported to cause PD peritonitis. Our study by necessity suffers from the limitations associated with a registry review including non-standardised microbiological methods and complexity in the confirmation of NTM as the causative agent of PD peritonitis. Further, because data regarding the diagnostic criteria are not submitted to ANZDATA we are unable to confirm that every patient fulfilled ISPD criteria. Data that were unavailable included the time to diagnosis, duration of antibiotics or reasons for removing or retaining the Tenckhoff catheter. Similarly, it is not recorded whether physician or patient preference, or complications arising from NTM peritonitis (such as abdominal adhesions), contributed to the observation that no patient whose Tenckhoff catheter was removed reconverted to PD.

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Conflict of interest The authors declare that they have not conflicts of interest.

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