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Systematic literature review of the diagnosis, prognosis, and treatment of peritoneal dialysis-related infection caused by nontuberculous mycobacteria

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Abstract

The number of peritoneal dialysis (PD) catheter-related infections and peritonitis caused by nontuberculous mycobacteria (NTM) has been increasing. Nonetheless, the optimal timing for the relocation of the exit site, removal and reinsertion of the PD catheter, prognosis, and duration of antibiotic treatment remain unclear. This literature review aimed to investigate the epidemiology of patient characteristics and evaluate the most effective diagnostic and treatment strategies for PD catheter-related infections and peritonitis caused by NTM. The systematic literature review was conducted on published cases of PD catheter-related infection and peritonitis caused by NTM in PubMed, Embase, and Ichushi databases up to August 2022. A total of 335 cases (64.1%, male; mean age, 53.4 years; mean dialysis duration, 25.4 months) were analyzed. The most common causative agent of infection was *Mycobacterium abscessus* (40.1%), followed by *Mycobacterium fortuitum* (24.8%) and *Mycobacterium chelonae* (16.6%). With respect to diagnosis, 42.9%, 28.1%, and 29.0% of cases were diagnosed as PD catheter-related infection only, peritonitis only, and both, respectively. The initial cultures were positive for NTM only, positive for any other bacteria, and negative for NTM only in 56.5%, 19.8%, and 23.7% of cases, respectively. Ultimately, more than 80% of cases were treated with multiple antibiotics. PD catheter removal was performed in 55.4% of patients with PD catheter-related infections only and 85.5% of those with PD peritonitis. PD continuation or resumption was possible in 62.2% and 16.0% of patients, respectively. In conclusion, our findings indicate that it is advisable to perform acid-fast bacilli stain and culture in order to promptly identify NTM. PD catheter removal may be an essential management strategy during the early stages of NTM infection.

Keywords Catheter-related infection, Catheter removal, Exit site infection, Nontuberculous mycobacteria, Peritonitis, Tunnel infection

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Background

Nontuberculous mycobacteria (NTM) are major components of the microflora in the environment. They cause soft tissue infection, osteomyelitis, surgical-site infection, and infections following the insertion of artificial materials [1]. Generally, diagnosing infections caused by NTM is not possible with routine bacterial cultures, and acid-fast bacilli stain, culture, or polymerase chain reaction (PCR) test is required.

Mycobacterium fortuitum (*M. fortuitum*), *Mycobacterium abscessus* (*M. abscessus*), and *Mycobacterium chelonae* (*M. chelonae*) are common NTM known to cause peritoneal dialysis (PD)-related infection (including PD catheter-related infection such as exit-site infection and tunnel infection) and PD-related peritonitis [2, 3]. Despite the increasing incidence and prevalence of catheter-related infection caused by NTM [3], their accurate diagnostic methods and appropriate management, especially with respect to the relocation of the exit site and catheter removal, remain unclear. Furthermore, their prognosis and the optimal duration of antibiotic treatment remain unclear. Accordingly, this literature review aimed to investigate the accurate diagnostic methods and most effective treatment for PD catheter-related infection and peritonitis caused by NTM.

Methods

Three authors independently reviewed the titles and abstracts of database records, retrieved full texts for eligibility assessment, and extracted data from these cases. A literature search was conducted in both the PubMed and Embase databases (up to August 15th, 2022) using the keywords (Supplement 1). Since numerous cases have also been reported in Japanese papers, we included articles published only in Japanese to allow further elucidation of the clinical characteristics of the disease. Japanese articles were searched in Ichushi, which is a major Japanese database, using the keywords shown in Supplement 1. We excluded articles other than case reports of PD-related NTM infection, duplicates retrieved from other databases, and abstracts not written in English or Japanese.

In our study, PD catheter-related infection referred to exit-site infection and tunnel infection. For diagnostic culture, cases were categorized into three groups. Group 1 comprised cases that yielded positive NTM culture in the initial attempt, including cases that tested positive for NTM only and cases that additionally tested positive for any other bacteria or fungi. Group 2 comprised cases in which the initial culture was positive for bacteria and/or fungi other than NTM, with subsequent cultures testing positive for NTM. Group 3 comprised cases in which the initial bacterial culture was negative, with subsequent cultures testing

Table 1 Characteristics of the included patients ($n=335$)

Characteristics	
Sex ($n=329$), Male, n (%)	211 (64.1)
Age, year ($n=310$)	53.4 ± 20.1
Cause of ESRD ($n=222$)	
DMN, n (%)	77 (34.7)
CGN, n (%)	54 (24.3)
HT, n (%)	30 (13.5)
Hypoplasia, n (%)	13 (5.8)
PKD, n (%)	7 (3.2)
PD duration, month ($n=247$)	25.4 ± 28.6
Past history of PD-related infection ($n=275$)	
PD catheter-related infection only, n (%)	71 (25.8)
PD-related peritonitis only, n (%)	13 (4.7)
Both PD catheter-related infection and PD-related peritonitis, n (%)	14 (5.1)
Past history of NTM infection ($n=267$)	14 (5.2)
Causative pathogen ($n=319$)	
M. abscessus, n (%)	128 (40.1)
M. fortuitum, n (%)	79 (24.8)
M. chelonae, n (%)	53 (16.6)
M. avium, n (%)	15 (4.7)
M. gordonae, n (%)	4 (1.3)
Diagnosis ($n=303$)	
PD catheter-related infection only, n (%)	130 (42.9)
PD-related peritonitis only, n (%)	85 (28.1)
Both PD catheter-related infection and PD-related peritonitis, n (%)	88 (29.0)
Initial culture result for diagnosis ($n=278$)	
[Group 1] positive for NTM, n (%)	157 (56.5)
[Group 2] positive for any other bacteria, n (%)	55 (19.8)
[Group 3] negative, n (%)	66 (23.7)
Antibiotics Therapy ($n=294$)	
Number of antimicrobial use	
0, n (%)	9 (3.1)
1, n (%)	49 (16.7)
2, n (%)	126 (42.9)
3, n (%)	93 (31.6)
4, n (%)	17 (5.8)
Types of antimicrobial use	
Macrolide antimicrobial use, n (%)	200 (68.0)
Aminoglycoside antimicrobial use, n(%)	156 (53.1)
Quinolone antimicrobial use, n (%)	146 (49.6)
Beta-lactam antimicrobial use, n (%)	132 (44.9)
Rifampicin antimicrobial use, n (%)	31 (10.5)
Tetracycline antimicrobial use, n (%)	29 (9.9)
Ethambutol antimicrobial use, n (%)	25 (8.5)
Linezolid/Tedizolid antimicrobial use, n (%)	14 (4.8)
Sulfamethoxazole Trimethoprim antimicrobial use, n (%)	11 (3.7)

Values are presented as mean ± SD or numbers (%)

Abbreviations: ESRD end-stage renal disease, *DMN* diabetic nephropathy, *CGN* chronic glomerulonephritis, *HT* hypertension, *PD* peritoneal dialysis, *NTM* nontuberculous mycobacteria

positive for NTM. Groups 2 and 3 also included cases that did not submit acid-fast bacilli stain or culture in the initial attempt. The number of antimicrobial use was counted as the maximum number of antibiotics effective against NTM that were prescribed simultaneously.

Results

This study included 335 cases of PD catheter-related infection and peritonitis caused by NTM, which were reported between 1983 and 2022 (Supplement 2). Supplement 3 shows the trend in the number of cases and papers in all three databases, whereas Supplement 4 presents the cases and papers published in Ichushi. Table 1 summarizes the characteristics of the included patients. Supplement 5 provides detailed information on the 335 cases of PD catheter-related infection and peritonitis caused by NTM.

The median age of the included patients was 53.4 years (range, 0.25–92 years); moreover, 211 (64.1%) patients were male. With respect to diagnosis, 130 cases (42.9%) had catheter-related infection only, 85 cases (28.1%) had peritonitis alone, and 88 cases (29.0%) developed both catheter-related infection and peritonitis. Among 278 cases, 157 (56.5%), 55 (19.8%), and 66 (23.7%) cases were categorized into Groups 1, 2, and 3, respectively. Among the Group 2 cases [4–6], antibiotic therapy was unsuccessful in treating infection caused by *Corynebacterium* species in several instances; these cases were ultimately diagnosed with NTM infection.

Figure 1 and Table 2 show the clinical course of 130 patients with PD catheter-related infection only without peritonitis. Overall, 32 individuals continued with antibiotic therapy alone, one of whom died. Three individuals underwent renal transplantation while bridging with hemodialysis. Finally, 79 patients continued or resumed PD. The average duration of antibiotic therapy was 3.8 months (range, 0–24 months). Out of 85 patients with peritonitis (Fig. 2; Table 3), 14 opted for antibiotic therapy alone; among these patients, five died. Seven individuals underwent relocation of the exit site, with catheter removal being performed eventually. Among them, six patients ultimately transitioned to hemodialysis (one underwent renal transplantation later), and one patient resumed PD following the reinsertion of the PD catheter. Out of 141 patients whose PD catheter was removed in the early infection stage, 8 died. Moreover, eight patients proceeded to renal transplantation while bridging with hemodialysis. Finally, 15 individuals underwent catheter reinsertion, with PD being resumed in 13 patients.

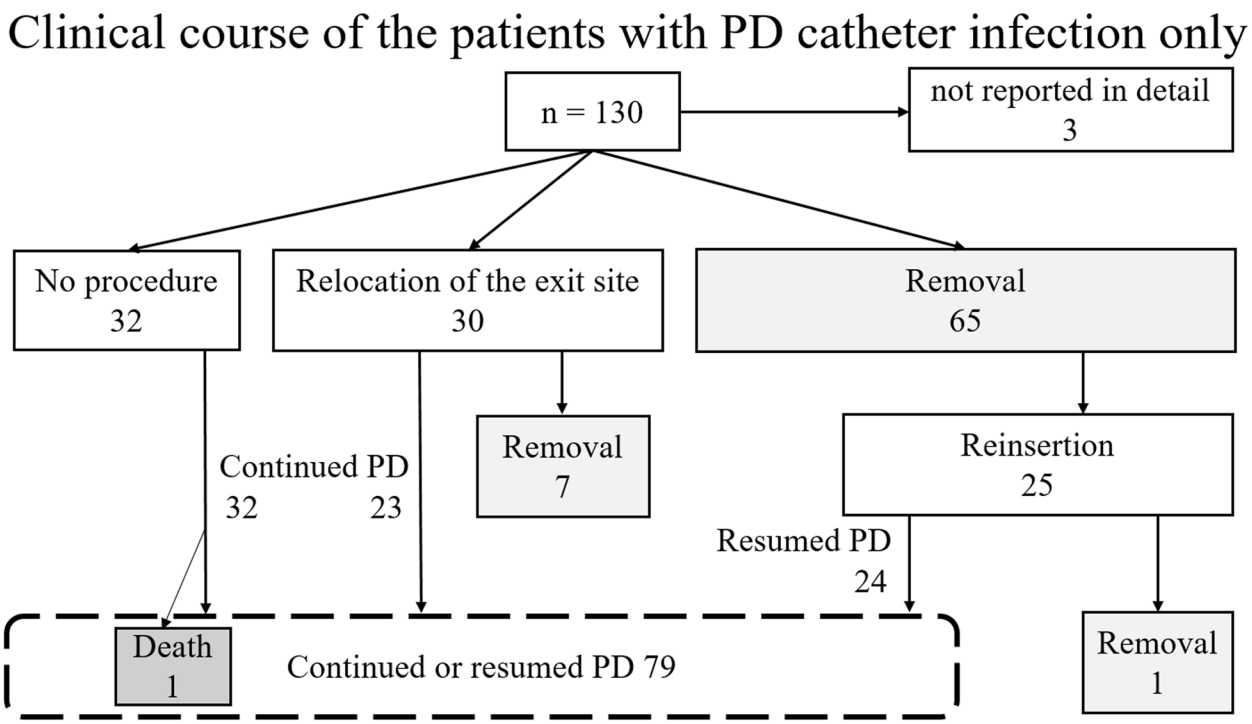

Fig. 1 Clinical course of patients with PD catheter-related infection only ($n = 130$). Out of 130 individuals with PD catheter-related infection only, 32 continued with antibiotic therapy alone, among whom one died. Moreover, 72 individuals ultimately underwent catheter removal, whereas 79 patients continued or resumed PD

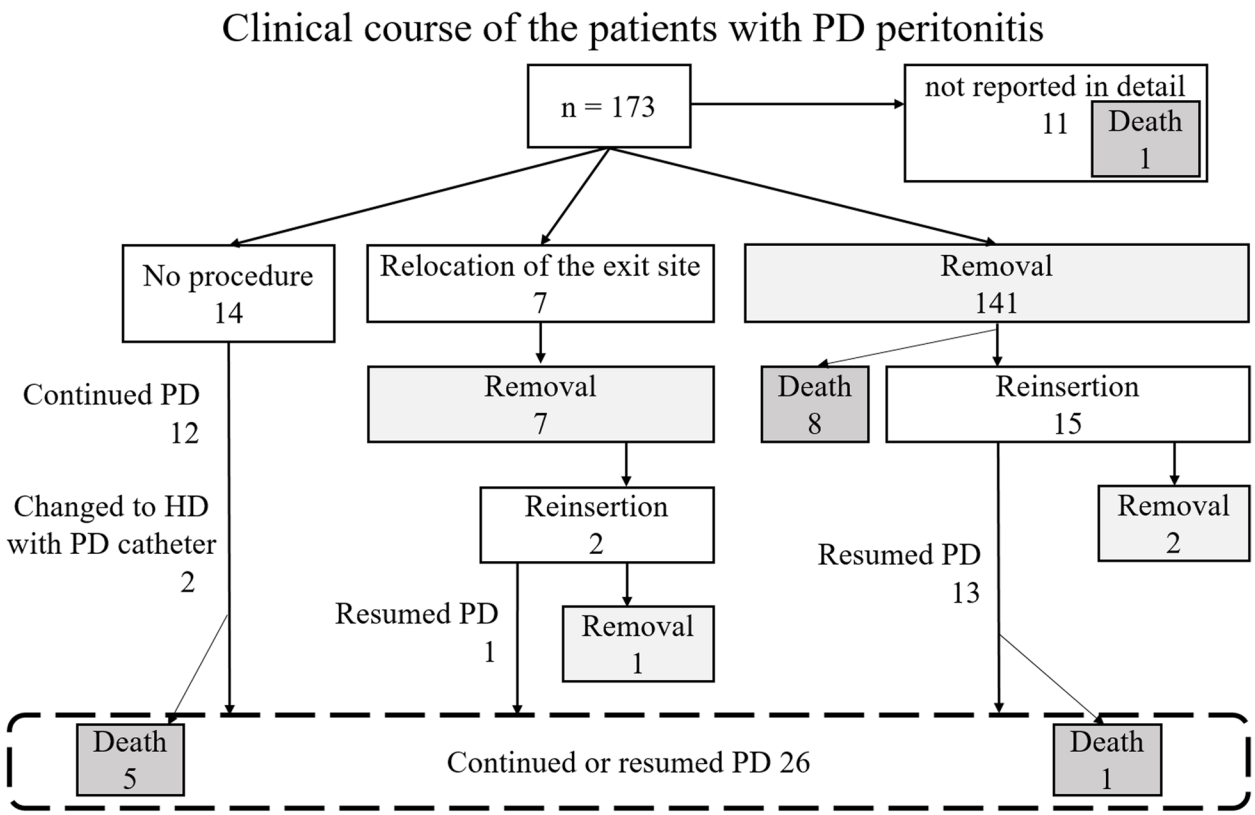

Fig. 2 Clinical course of patients with PD-related peritonitis ($n = 173$). Among patients with PD-related peritonitis, clinical follow-up was possible for 162 individuals. Fourteen patients opted for antibiotic therapy alone; among these patients, five died. Seven individuals initially underwent relocation of the exit site; however, they all eventually underwent catheter removal. PD catheter removal was performed in 141 patients, with eight fatalities noted. Catheter reinsertion was performed in 15 individuals, and 13 patients resumed PD; however, one patient died

Discussion

To our knowledge, this is the first report on the etiology, treatment, and prognosis of catheter-related infection and peritonitis caused by NTM. Regarding the pathogens involved, *M. fortuitum* and *M. chelonae* account for one-third of reported cases of PD-related peritonitis [2]. In our study, M. abscessus, which is the most common NTM [7], accounted for 40.1% of cases.

Previous reports have indicated that 70%, 20%, and 10% of NTM infections are diagnosed within 14, 21, and 28 days, respectively [8]. If acid-fast bacilli culture is not submitted in the initial attempt, diagnosis may take additional time. This suggests that NTM infections pose a challenge in diagnosis. In our study, cases were categorized into three groups according to diagnostic approaches or methods. With respect to the classification of cultures for diagnosis, Group 2 primarily comprised two types of diagnoses. The first type comprised patients who initially presented with bacterial peritonitis, which later progressed to a secondary NTM infection. The second type involved cases in which NTM infection could have been diagnosed using acid-fast stain but was initially misdiagnosed or undiagnosed when only gram stain was performed. Cases initially diagnosed as infections caused by *Corynebacterium* species, which exhibit a gram-stain appearance similar to that of NTM, were ultimately diagnosed as NTM infection due to the presence of acid-fast bacilli in the stain or culture. These cases might have originally belonged to Group 2, suggesting the importance of considering acid-fast stain to accurately diagnose NTM infections and ensure appropriate treatment. A previous study described this misidentification of NTM as ghost mycobacteria [9], with patients being initially treated for bacterial PD-related infection. However, they were found to have NTM-related infection following treatment failure. For patients who show a poor response to antibiotics targeting gram-positive rods, such as *Corynebacterium* sp. or *C. diphtheriae*, it is important to perform acid-fast bacilli stain, followed by mycobacterium culturing or a PCR test in order to promptly detect NTM [3]. In the present study, patients with peritonitis caused by NTM showed high rates of PD discontinuation and mortality. Since many cases of catheter-related infection progress to peritonitis, early diagnosis and

Table 2 Characteristics, treatment and prognosis of the included patients with PD catheter-related infection only ($n=127$)

Characteristics		Average duration of antibiotic treatment [months]	All-cause mortality, *n*
Past history of PD-related infection ($n=105$)	43 (41.0)		
Past history of NTM infection ($n=101$)	2 (2.0)		
Treatment ($n=127$)			
Antimicrobial therapy only, n (%)	32 (25.2)	4.6 ± 3.7	1 (3.1)
Relocation of the exit site, n (%)	23 (18.1)	2.5 ± 3.6	0
Relocation of the exit site and removal, n (%)	7 (5.5)	3.0	0
Removal, n (%)	40 (31.5)	4.2 ± 5.1	0
Removal and reinsertion, n (%)	24 (18.9)	2.7 ± 1.7	0
Removal, reinsertion, and removal, n (%)	1 (0.8)	14	0
All of the above	127	3.8 ± 4.1	1 (0.08)
Number of antimicrobial use ($n=108$)			
0, n (%)	6 (5.6)		
1, n (%)	13 (12.0)		
2, n (%)	50 (46.3)		
3, n (%)	35 (32.4)		
4, n (%)	4 (13.7)		
Continued or resumed PD, n (%)	79 (62.2)	N/A	1 (1.3)

Values are presented as mean ± SD or numbers (%)

Abbreviations: *N/A* not applicable, *PD* peritoneal dialysis

The number of patients whose duration of antibiotic treatment was reported: 18 (antimicrobial therapy only), 17 (relocation of the exit site), 1 (relocation of the exit site and removal), 13 (removal and reinsertion), 1 (removal, reinsertion, and removal)

therapeutic intervention upon the occurrence of catheter-related infection are crucial.

In our review, more than 80% of cases were treated with combination therapy with multiple antibiotics, including macrolides, fluoroquinolones, carbapenems, tetracyclines, and aminoglycosides (Table 1). Although the FDA currently warns against the use of fluoroquinolones, infections caused by gram-negative rods have long been treated with fluoroquinolones as the first-choice medications. Notably, fluoroquinolones are partially effective against NTM infection, sometimes resulting in the induction of highly resistant strains, even in patients with a history of PD catheter-related infection. In our study, 25.2% and 8.6% of patients with PD catheter-related infection and peritonitis, respectively, were conservatively managed using antimicrobial therapy only. There remain no established guidelines for catheter removal in cases of tunnel infections caused by NTM; further, treatment approaches significantly vary across facilities. Although our findings do not confirm the validity of catheter removal, extended use of multiple antibiotics in patients with PD-related infection results in an increased risk of side effects [7]. Moreover, patients with renal dysfunction have an increased risk of strong side effects from antibiotics [10]. For example, fluoroquinolones involve risks of enteritis, Achilles tendon rupture, and malignant arrhythmias [10]. Macrolides can cause gastrointestinal symptoms and cardiovascular-related death [11]. Tetracyclines may cause pigment deposition and gastrointestinal symptoms, whereas aminoglycosides carry the risk of renal and hearing impairment. The average duration of antibiotic therapy was 3.8 and 6.0 months in patients with PD catheter-related infection and peritonitis, respectively. However, given the lack of randomized controlled trials, further prospective studies investigating and validating the potential impact of treatment duration on prognosis are required.

Notably, 15 (8.7%) patients with PD-related peritonitis died (Fig. 2), whereas only one (0.8%) patient with PD catheter-related infection died (Fig. 1). Regarding the continuation of PD, 79 (62.2%) and 26 (16.0%) of patients with PD catheter-related infection and peritonitis, respectively, continued/resumed PD. In the former group, almost half of the patients tolerated conservative multiple-antibiotic therapy; however, one patient died. All patients who underwent surgical intervention (including relocation of the exit site or removal and reinsertion) survived with PD. This could be attributed to early intervention preventing the progression of catheter-related infection to peritonitis [12, 13]. Consistent with current guidelines [2, 3], our findings indicate that patients with PD-related peritonitis should undergo immediate catheter removal.

Table 3 Characteristics, treatment and prognosis of the included patients with PD-related peritonitis ($n = 162$)

Characteristics		Average duration of antibiotics [month]	All cause of death, *n*
Past history of PD-related infection ($n = 144$)			
PD catheter-related infection, n (%)	43 (41.0)		
PD-related peritonitis only	29 (20.1%)		
Past history of NTM infection ($n = 145$)	10 (6.9%)		
Abdominal fluid cell count on diagnosis ($n = 95$)			
1000 > /ml, n (%)	37 (38.9%)		
Treatment			
Antimicrobial therapy only, n (%)	14 (8.6)	6.3 ± 7.0	5 (35.7)
Relocation of the exit site and removal, n (%)	5 (3.1)	11.0 ± 8.7	0 (0)
Relocation of the exit site, removal and reinsertion, n (%)	1 (0.6)	N/A	0 (0)
Relocation of the exit site, removal, reinsertion and removal, n (%)	1 (0.6)	0	0 (0)
Removal, n (%)	126 (77.8)	5.9 ± 4.2	8 (6.3)
Removal and reinsertion, n (%)	13 (8.0)	3.8 ± 2.4	1 (7.7)
Removal, reinsertion and removal, n (%)	2 (1.2)	11	0 (0)
All of the above	162	6.0 ± 5.0	14 (8.6)
Number of antimicrobial use ($n = 154$)			
0, n (%)	1 (0.6)		
1, n (%)	26 (16.9)		
2, n (%)	61 (39.6)		
3, n (%)	56 (36.4)		
4, n (%)	10 (6.5)		
Continued or resumed PD, n (%)	26 (16.0)	5.6 ± 6.0	6 (23.1)

Values are presented as mean ± SD or numbers (%)

Abbreviations: *N/A* not applicable, *PD* peritoneal dialysis

The number of patients whose duration of antibiotic treatment was reported: 12 (antimicrobial therapy only), 4 (relocation of the exit site and removal), 0 (relocation of the exit site, removal, and reinsertion), 70 (removal), 7 (removal and reinsertion), 1 (removal, reinsertion, and removal), 18 (continued or resumed PD)

This study has several limitations. First, given its retrospective design, certain items had missing values, which impeded correct evaluation. Regarding culture submission, it was unclear in some cases whether both general bacterial culture and acid-fast bacterial culture were submitted in the initial attempt. Moreover, the timing of PD catheter surgery varied across the patients. In some cases, relocation of the exit site was initially performed for the diagnosis of catheter infection; however, there were cases where PD-related peritonitis occurred during the course. Moreover, we cannot completely avoid several bias types, including published bias and selective bias. Regarding PD peritonitis, the diagnostic criteria are consistent with no heterogeneity, however, improvements in culture techniques and proper sample collection have been emphasized since 2000. For catheter-related infections, the introduction of culture testing and ultrasound examination was first recommended in 2005, suggesting that cases prior to this may not have been accurately diagnosed. Second, we did not thoroughly consider risk factors for NTM infection, such as a history of PD-related infection, presence of positive gram-positive rods in the bacterial culture, and unresponsiveness to antibiotic therapy. Further studies are warranted to elucidate these risk factors. Finally, the safety of and optimal duration until PD catheter reinsertion could not be elucidated because of the limited number of included cases.

Conclusions

Our findings indicate that it is advisable to promptly perform acid-fast bacilli stain and culture when PD catheter-related infection caused by NTM is suspected. Moreover, temporal catheter removal may be an appropriate management strategy during the early stages of PD catheter-related infection caused by NTM.

Abbreviations

NTM nontuberculous mycobacteria

PCR polymerase chain reaction
PD peritoneal dialysis

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-024-03841-2.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

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Clinical trial number
Not applicable.

Authors' contributions
N.K., K.I., and Y.K. researched the literature and conceived the study. N.K. and K.I. were involved in protocol development, ethics approval acquisition, and data analysis. N.K. and K.I. wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the local institutional ethical review board (Helsinki committee) of St. Luke's International Hospital/University. The requirement for informed consent was waived by the ethical review board (Helsinki committee) of St. Luke's International Hospital/University owing to the retrospective nature of this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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