Renal Replacement Therapy

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A retrospective study of patients with *Stenotrophomonas maltophilia* peritonitis undergoing peritoneal dialysis

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Abstract

Background *Stenotrophomonas maltophilia* (*S. maltophilia*) is being increasingly recognized as an important cause of nosocomial infections, particularly in immunocompromised patients, such as patients undergoing dialysis. *S. maltophilia* peritonitis is strongly associated with the loss of peritoneal catheter among patients undergoing peritoneal dialysis (PD) owing to its resistance to different groups of antibiotics. Thus, the aim of this study was to investigate the characteristics of and risk factors for *S. maltophilia* peritonitis in patients undergoing PD.

Methods This single-center, retrospective, case–control study was conducted between April 2013 and October 2022. Patients who were undergoing PD at Kawashima Hospital and were diagnosed with *S. maltophilia* peritonitis were included in this study. Controls were randomly selected from among patients who were undergoing PD and were diagnosed with peritonitis caused by microorganisms other than *S. maltophilia*. The demographic data, clinical characteristics, and initial treatment data of the patients were analyzed to determine the risk factors for PD-related *S. maltophilia* peritonitis.

Results Five patients with *S. maltophilia* peritonitis and 15 controls (three controls to one case) were included in this study. The incidence of *S. maltophilia* peritonitis was significantly more frequent among patients with diabetes mellitus (80.0% vs. 20.0%; $p=0.031$) and among patients with higher white blood cell counts in the dialysate after appropriate antibiotic therapy (2561/μL [349–4654/μL] vs. 20/μL [20–23/μL]; $p=0.0006$) than among the control patients. Although all the patients were treated with appropriate antibiotics after the identification of *S. maltophilia*, they had a significantly higher rate of catheter removal than the controls (80.0% vs. 0.0%; $p=0.001$).

Conclusions Diabetes mellitus may be an important risk factor for *S. maltophilia* peritonitis in patients undergoing PD.

Keywords *Stenotrophomonas maltophilia*, Peritoneal dialysis, Peritonitis, Diabetes mellitus, Catheter removal

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Background

Stenotrophomonas maltophilia (*S. maltophilia*) is an aerobic, gram-negative organism with intrinsic multi-drug resistance. *S. maltophilia* is being increasingly recognized as an important cause of nosocomial infections, particularly in immunocompromised patients [1]. Clinical manifestations of *S. maltophilia* infection include bacteremia, endocarditis, respiratory infections, urinary tract

infections, and peritonitis [1]. Patients undergoing dialysis are ideal targets for infections because they are immunosuppressed. In addition, the prosthetic grafts and central venous or peritoneal catheters required for dialysis can serve as artificial access points for infectious organisms. Peritoneal dialysis (PD)-related peritonitis is a major cause of hospitalization and catheter removal or hemodialysis transfer in patients undergoing PD [2]. *S. maltophilia* peritonitis is a rare complication of PD that may result in mortality or catheter loss [3]. However, to our knowledge, there is no case series on *S. maltophilia* peritonitis among patients in Japan. Therefore, the aim of this study was to examine the characteristics of and risk factors for peritonitis caused by *S. maltophilia* in patients undergoing PD.

Methods

Study population

This was a single-center, retrospective, case–control study that aimed to investigate the risk factors for PD-related peritonitis, particularly peritonitis caused by *S. maltophilia*. We retrospectively selected cases of peritonitis caused by *S. maltophilia* in patients who underwent PD between April 2013 and October 2022 at our institution. *S. maltophilia* peritonitis was defined as the presence of characteristic clinical features, including peritonitis, dialysate leukocytosis (white blood cell count > 100/μL with neutrophil count > 50%), and growth of *S. maltophilia* in the dialysate culture. Controls were randomly selected from among patients who underwent PD during the same period and were diagnosed with peritonitis caused by microorganisms other than *S. maltophilia*, i.e., their dialysate cultures showed growth of microorganisms other than *S. maltophilia*. Fifteen controls were matched to each case as far as possible for age and sex on a 3:1 basis.

Data collection

Clinical data, including sex, age, duration of dialysis, number of previous peritonitis episodes, microorganisms in dialysate cultures, presence of diabetes mellitus and cardiovascular disease, body temperature, blood pressure, and laboratory data at the time of the hospital visit were collected by reviewing the patients' medical records. Laboratory data included white blood cell and platelet counts; hemoglobin, urea nitrogen, creatinine, total protein, serum albumin, serum aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, sodium, potassium, corrected calcium, phosphate, β_2-microglobulin, and C-reactive protein levels and dialysate white blood cell counts.

Statistical analysis

Data were expressed as mean ± standard deviation or median (interquartile range), as appropriate. Categorical variables were evaluated using Fisher's exact test, whereas continuous variables were compared using Student's *t*-test or Mann–Whitney *U* test, as appropriate. All analyses were performed using JMP, version 16 (SAS Institute Inc., Cary, NC, USA). $p < 0.05$ was considered statistically significant.

Results

Demographic and clinical characteristics of the patients

A total of 372 peritonitis cases were recorded during the study period. Among these, five were caused by *S. maltophilia*, accounting for approximately 1.3% of all the peritonitis cases. Thus, five patients with *S. maltophilia* peritonitis who were undergoing PD were included in the analysis. Fifteen controls (three controls to one case) were included as well. The baseline demographic and clinical characteristics of the five patients are listed in Table 1. The mean age of the patients was 66 years, and four were male. The primary cause of end-stage renal disease in four of the five patients was diabetic nephropathy. None of the patients had any concomitant exit site or tunnel infection. *S. maltophilia* and *Enterococcus faecalis* (*E. faecalis*) were isolated from the dialysate culture of one of the patients, indicating that the patient had a polymicrobial infection. The courses of antibiotic treatment and outcomes are listed in Table 1. After identification of the causative organism in each case, all the patients were properly treated using antibiotics that are sensitive to *S. maltophilia*. However, the peritoneal effluent of four patients did not clear up, resulting in the removal of their peritoneal catheters.

Clinical and laboratory characteristics of the patients and controls

Table 2 shows the results of the case–control analysis. The rate of peritonitis caused by *S. maltophilia* was significantly higher among patients with diabetes mellitus (80.0% vs. 20.0%; $p = 0.031$) and among patients with higher dialysate cell counts after appropriate antibiotic therapy (2561/μL [349–4654/μL] vs. 20/μL [20–23/μL]; $p = 0.0006$) than among the control patients. In addition, the rate of catheter removal among the patients was significantly higher than that among the controls (80.0% vs. 0%; $p = 0.001$). However, there were no significant differences in other characteristics between the patients and controls.

Table 1 Demographic and clinical characteristics of PD patients with *Stenotrophomonas maltophilia* peritonitis

No.	1	2	3	4	5
Age (years)/Sex	63/M	64/M	53/M	71/M	79/F
Dialysis duration (months)	11.8	13.3	15.0	10.2	4.7
Primary KD	DN	DN	DN	DN	Unknown
Number of previous peritonitis episodes	0	1	0	0	1
Concomitant exit site or tunnel infection	–	–	–	–	–
Polymicrobial infection	–	–	*Enterococcus faecalis*	–	–
Antibiotic therapy	CEZ + ISP → VCM + MEPM → CAZ + PZFX → MINO + LVFX + TMP–SMX	MINO + PZFX + TMP–SMX → PZFX + TMP–SMX + FLCZ	CEZ + ISP → VCM + MEPM → VCM + PZFX	CEZ + ISP → VCM + MEPM → PZFX + RFP → CAZ + RFP	CEZ + ISP → PZFX
Outcome	Continued PD	Catheter removal	Catheter removal	Catheter removal	Catheter removal

M male; *F* female; *KD* kidney disease; *DN* diabetic nephropathy; *BMI* body mass index; *CEZ* cefazolin; *ISP* isepamicin; *VCM* vancomycin; *MEPM* meropenem; *CAZ* ceftazidime; *PZFX* pazufloxacin; *MINO* minocycline; *LVFX* levofloxacin; *TMP–SMX* trimethoprim–sulfamethoxazole; *FLCZ* fosfluconazole; *RFP* rifampicin

Table 2 Clinical and laboratory characteristics of PD patients in cases and controls

Variables	Cases ($n=5$)	Controls ($n=15$)	p
Male, *n* (%)	4 (80.0)	12 (80.0)	1.00
Age (years)	66.0 ± 9.7	66.0 ± 7.8	1.00
BMI (kg/m^2)	25.2 ± 1.8	23.1 ± 2.9	0.154
Dialysis duration (days)	11.8 [7.5–14.2]	18.0 [8.5–46.8]	0.22
Diabetes mellitus, *n* (%)	4 (80.0)	3 (20.0)	0.031*
Cardiovascular disease, *n* (%)	4 (80.0)	4 (26.7)	0.109
Body temperature (℃)	37.1 [36.5–37.3]	37.0 [36.6–37.2]	0.85
Systolic blood pressure (mmHg)	145 [125–151]	125 [108–141]	0.29
Diastolic blood pressure (mmHg)	75 [71–80]	76 [69–83]	1.00
White blood cell (/μL)	8100 [5900–10350]	9600 [7900–14100]	0.176
Hemoglobin (g/dL)	9.6 ± 1.4	11.0 ± 1.6	0.127
Platelet (× 10^4/μL)	29.1 [22.7–34.3]	20.9 [18.4–22.3]	0.067
Urea nitrogen (mg/dL)	38.9 [32.7–56.8]	39.7 [31.3–51.0]	0.86
Creatinine (mg/dL)	9.3 ± 2.5	9.3 ± 3.4	0.79
Total protein (g/dL)	5.8 ± 0.57	6.4 ± 0.98	0.23
Albumin (g/dL)	2.6 [2.4–3.2]	3.3 [2.5–3.6]	0.20
Aspartate aminotransferase (U/L)	20 [11–27]	19 [13–24]	0.97
Alkaline phosphatase (U/L)	225 [164–348]	261 [194–285]	0.76
Lactate dehydrogenase (U/L)	193 [173–271]	207 [183–216]	0.80
Sodium (mmol/L)	135 [131–139]	136 [133–140]	0.38
Potassium (mmol/L)	3.7 [3.3–4.4]	3.5 [3.3–4.3]	0.83
Corrected calcium (mg/dL)	9.5 ± 0.47	9.1 ± 0.67	0.38
Phosphate (mg/dL)	4.5 [3.3–5.8]	4.0 [3.4–5.3]	0.76
C-reactive protein (mg/dL)	2.7 [1.1–6.7]	0.92 [0.47–4.3]	0.22
Hemoglobin A1c (%)	6.1 ± 0.65	5.8 ± 0.61	0.64
Cell counts of dialysate at diagnosis of peritonitis (/μL)	2670 [1145–8709]	3515 [965–7900]	1.00
Cell counts of dialysate after appropriate antibiotics (/μL)	2561 [349–4654]	20 [20–23]	0.0006*
β_2-microglobin (μg/L)	29.4 [25.2–30.5]	23.1 [20.5–30.3]	0.38
Catheter removal, *n* (%)	4 (80.0)	0 (0.0)	0.001*

* $p<0.05$ when comparing cases versus controls

BMI Body mass index

Table 3 Susceptibility of *Stenotrophomonas maltophilia* isolated from the dialysate in each patient to antibiotics

No.	1		2		3		4		5	
Ampicillin/sulbactam		–		–		R		R		R
Cefazolin	≧32	R	≧32	R		R		R		R
Ceftriaxone		–		–	≧64	R	≧64	R	≧64	R
Ceftazidime	≦4	S	≦4	S	≦4	S	≦4	S	8	S
Meropenem		–		–	≧16	R	≧16	R	≧16	R
Vancomycin		–		–		–		–	–	–
Fosfomycin	≧32	R	≧32	R	≧32	R	≧32	R	≧32	R
Amikacin	≧64	R	≧64	R	16	R	32	R	≧64	R
Isepamicin		R		R		R		R		R
Minocycline	≦2	S	≦2	S	≦2	S	≦2	S	≦2	S
Levofloxacin		–		–	≦0.5	S	≦0.5	S	1	S
Cefotiam	≧32	R	≧32	R		R		R		R
Latamoxef		R		S		R		R		R
Imipenem/cilastatin	≧16	R	≧16	R	≧16	R	≧16	R	≧16	R
Ofloxacin		S		S		S		S		S
Ciprofloxacin	1	S	2	I	1	S	≦0.25	S	2	I

I intermediate; *R* resistant; *S* susceptible

Antimicrobial susceptibility of *S. maltophilia*

The antimicrobial susceptibility profile of *S. maltophilia* in each case is presented in Table 3. *S. maltophilia* was susceptible to ceftazidime, minocycline, levofloxacin, and ofloxacin in all cases.

Discussion

We examined the characteristics of *S. maltophilia* peritonitis in patients undergoing PD. The results revealed a relationship between diabetes mellitus and *S. maltophilia* peritonitis in patients undergoing PD. Use of broad-spectrum antibiotics, immunosuppressive therapy, prolonged hospitalization, malignant lesions, and central venous catheterization are considered risk factors for *S. maltophilia* infection [1, 3]. In the present study, all the five patients with *S. maltophilia* peritonitis did not have these predisposing conditions. Diabetes mellitus has also been reported to be a predisposing factor for *S. maltophilia* peritonitis in a previous study [4]. However, all the five patients with *S. maltophilia* peritonitis included in that study had diabetes mellitus; therefore, their results were not sufficient to conclude that diabetes mellitus is a predisposing factor for *S. maltophilia* peritonitis.

S. maltophilia is an uncommon pathogen of PD-related peritonitis. Very few case–control studies of *S. maltophilia* peritonitis have been conducted [3, 4]. The authors of these previous studies reported that the patients with *S. maltophilia* peritonitis were younger, more likely to be on immunosuppressive therapy, and had lower hemoglobin levels than controls. The present study is the first to show that diabetes mellitus could be a predisposing factor for *S. maltophilia* peritonitis. This is particularly noteworthy because we compared patients with *S. maltophilia* with those with peritonitis caused by microorganisms other than *S. maltophilia*. Patients undergoing PD, especially those with diabetic nephropathy, are more likely to have multifactorial immune defects associated with uremia and other comorbidities, such as diabetes [5, 6], which may lead to *S. maltophilia* peritonitis.

The rate of *S. maltophilia* peritonitis at our institution is approximately 1.3%, which is similar to the rates reported in previous studies [7]. A review of the literature (extracted from PubMed) on *S. maltophilia* peritonitis in patients undergoing PD is summarized in Table 4 [3, 4, 7–14]. Although for approximately half of the patients in these studies there was no information on primary kidney disease, it can be concluded that patients undergoing PD who have *S. maltophilia* peritonitis tend to have diabetes. The total rate of catheter removal in these studies was 60.6% (20 out of 33 cases). Although all the patients in the present study received appropriate antibiotic therapy after the identification of *S. maltophilia*, the rate of catheter removal among the patients was significantly higher than that among the controls.

S. maltophilia is usually resistant to many classes of antibiotics, such as cephalosporins, carbapenems, and aminoglycosides [1]. The main mechanism underlying the resistance of *S. maltophilia* to antibiotics is the presence of gene-encoding efflux pumps and antibiotic-inactivating enzymes [15]. The International Society for Peritoneal Dialysis (ISPD) peritonitis guidelines recommend

Table 4 Cases of *Stenotrophomonas maltophilia*-related peritonitis in PD patients in the literature

No.	Author	Age/sex	Dialysis duration (months)	Primary KD	Diabetes mellitus	No. of previous peritonitis episodes	Antibiotic therapy	Outcome
1	Szeto et al. [7]	NA	NA	NA	NA	0	VCM + IPM → CAZ + GM → CPFX	Catheter removal
2	Szeto et al. [7]	NA	NA	NA	NA	1	VCM + IPM → CAZ → CPFX → TMP–SMX	Catheter removal
3	Szeto et al. [7]	NA	NA	NA	NA	3	VCM + IPM → CAZ	Catheter removal
4	Szeto et al. [7]	NA	NA	NA	NA	1	VCM + IPM → CAZ → CPFX	Catheter removal
5	Szeto et al. [7]	NA	NA	NA	NA	2	VCM + IPM → CAZ + NTL	Catheter removal
6	Szeto et al. [7]	NA	NA	NA	NA	0	VCM + IPM → CAZ → ABPC	Catheter removal
7	Taylor et al. [3]	61/M	60	NA	NA	1.6	NA	Continued PD
8	Taylor et al. [3]	64/M	9	NA	NA	1.3	NA	Continued PD
9	Taylor et al. [3]	52/F	26	NA	NA	0.0	NA	Catheter removal
10	Taylor et al. [3]	19/F	68	NA	NA	0.9	NA	Catheter removal
11	Taylor et al. [3]	16/F	6	NA	NA	2.0	NA	Catheter removal
12	Taylor et al. [3]	43/F	99	NA	NA	0.7	NA	Continued PD
13	Taylor et al. [3]	16/M	1	NA	NA	0.0	NA	Catheter removal
14	N. Al-Hilali et al. [8]	63/M	43	DN	(+)	4	VCM + GM CAZ + CPFX	Catheter removal
15	N. Al-Hilali et al. [8]	65/F	19	DN	(+)	2	VCM + GM CAZ + CPFX	Catheter removal
16	Cheng et al. [9]	47/M	NA	NA	NA	NA	NA	Catheter removal
17	Baek et al. [4]	61/F	32	DN	(+)	3	CEZ + TOB → CAZ + AMK → CAZ + AMK + PIPC	Continued PD
18	Baek et al. [4]	34/F	24	DN	(+)	1	CEZ + TOB	Continued PD
19	Baek et al. [4]	48/F	15	DN	(+)	2	VCM + CAZ + CPFX → CAZ → TMP–SMX + CTRX + CPFX → AMPH-B	Catheter removal
20	Tzanetou K et al. [10]	60/M	96	Nephrolithiasis	NA	Repeatedly	CAZ + TMP–SMX	Continued PD
21	Tzanetou K et al. [10]	64/F	120	PKD	NA	2	CAZ + AMK → TMP–SMX	Continued PD
22	Tzanetou K et al. [10]	64/F	96	CGN	NA	0	VCM + CAZ → AMK + CPFX + TMP–SMX	Continued PD
23	Tzanetou K et al. [10]	64/F	96	CGN	NA	1	TMP–SMX	Continued PD
24	Tzanetou K et al. [10]	40/M	96	Nephrolithiasis	NA	0	TMP–SMX + TIPC/CVA	Catheter removal
25	Machuca E et al. [11]	54/F	23	Alport disease	NA	0	VCM + CAZ → TMP–SMX + AMK	Continued PD
26	Lee et al. [12]	NA	NA	NA	NA	NA	NA	Continued PD
27	Azak A et al. [13]	57/F	36	DN	(+)	0	VCM + CAZ → CAZ + LVFX	Continued PD
28	Beatriz Millan- Diaz et al. [14]	54/M	NA	Calcineurin toxicity	NA	3	VCM + CAZ + FLCZ → TMP–SMX	Catheter removal

Table 4 (continued)

No.	Author	Age/sex	Dialysis duration (months)	Primary KD	Diabetes mellitus	No. of previous peritonitis episodes	Antibiotic therapy	Outcome
29	Our study	63/M	12	DN	(+)	0	CEZ + ISP → VCM + MEPM → CAZ + PZFX → MINO + LVFX + TMP–SMX	Continued PD
30	Our study	64/M	13	DN	(+)	1	MINO + PZFX + TMP–SMX → PZFX + TMP–SMX + FLCZ	Catheter removal
31	Our study	53/M	15	DN	(+)	0	CEZ + ISP → VCM + MEPM → VCM + PZFX	Catheter removal
32	Our study	71/M	10	DN	(+)	0	CEZ + ISP → VCM + MEPM → PZFX + RFP → CAZ + RFP	Catheter removal
33	Our study	79/F	5	Unknown	(−)	1	CEZ + ISP → PZFX	Catheter removal

M male; *F* female; *NA* not available; *KD* primary kidney disease; *DN* diabetic nephropathy; *PKD* polycystic kidney disease; *CGN* chronic glomerulonephritis; *VCM* vancomycin; *IPM* imipenem; *CAZ* ceftazidime; *GM* gentamycin; *CPFX* ciprofloxacin; *TMP–SMX* trimethoprim–sulfamethoxazole; *NTL* netilmicin; *ABPC* ampicillin; *CEZ* cefazolin; *TOB* tobramycin; *AMK* amikacin; *PIPC* piperacillin; *CTRX* ceftriaxon; *AMPH-B* amphotericin B; *TIPC/CVA* clavulanic acid/ticarcillin; *LVFX* levofloxacin; *ISP* isepamicin; *MEPM* meropenem; *PZFX* pazufloxacin; *MINO* minocycline; *FLCZ* fosfluconazole; *RFP* rifampicin; *PD* peritoneal dialysis

that *S. maltophilia* peritonitis be treated with two different classes of antibiotics for at least 3 weeks, with one of the antibiotics being trimethoprim–sulfamethoxazole [16]. Most cases of successful treatment of *S. maltophilia* peritonitis involve a combination of therapy with different antibacterial drugs (Table 4). In our cohort, only one patient, treated in accordance with the ISPD peritonitis guidelines, could continue PD. In addition to antibiotic resistance, *S. maltophilia* forms a biofilm on the host surface [17]. Infections caused by biofilm-producing bacteria are difficult to treat and eradicate because they rarely respond to conventional antibiotic treatments. Therefore, peritoneal catheters should be removed early in cases of failure to respond to treatment [7]. *S. maltophilia* is frequently accompanied by gram-positive bacteria, mainly *E. faecalis* [18]. *S. maltophilia* and *E. faecalis* were both isolated from the dialysate culture of one of the patients in the present study. Therefore, clinicians should always keep in mind that *S. maltophilia* may not be the only pathogen involved in peritonitis. The ISPD peritonitis guidelines recommended cefazolin plus ceftazidime or cefepime monotherapy as an empiric treatment [16]. Because *S. maltophilia* is sensitive to ceftazidime, this empiric treatment may improve the clinical outcomes of patients with *S. maltophilia* peritonitis.

The main limitation of this study is that it was a single-center retrospective study with a small sample size, which may have concealed clinically significant differences between the patients and the controls. Therefore, further multicenter prospective studies are needed to confirm the findings of this study.

Conclusions

Diabetes mellitus may be an important risk factor for *S. maltophilia* peritonitis in patients undergoing PD.

Abbreviations

PD Peritoneal dialysis
ISPD International Society for Peritoneal Dialysis

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Author contributions

HS drafted the first manuscript. HS, MT, TI, MI, SW, TD, KO, and JM managed the patient. HS, TO, MT, TI, MI, SW, TD, KO, and JM performed the literature search. TO, MT, TI, MI, SW, TD, KO, and JM coordinated the data analysis and critically commented on the manuscript. TO, SW, TD, KO, and JM helped with writing the manuscript. All authors participated in discussions and read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethical Committee of Kawashima Hospital (approval no. 1119) and was conducted in accordance with the principles of the Declaration of Helsinki and Japanese ethical guidelines. All patients granted informed consent for their data to be included in this study.

Consent for publication

Not applicable.

Competing interests
The authors declare that they have no competing interests.

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