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Clinical Characteristics of *Stenotrophomonas maltophilia* Bacteremia: A Regional Report and a Review of a Japanese Case Series

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Abstract

Objective *Stenotrophomonas maltophilia* is an emerging nosocomial pathogen that causes fatal infections in critically ill or immunocompromised patients. *S. maltophilia* bacteremia (SMB) is a rare condition, and its clinical characteristics in Japanese settings are not well known.

Methods The medical charts of patients with SMB were retrospectively reviewed at two medical facilities (Okayama University Hospital and Tsuyama Chuo Hospital) for seven years. The data were analyzed along with those previously reported from other Japanese facilities.

Result A total of 181 patients (110 men and 71 women) were evaluated. The major underlying diseases included hematologic malignancy (36.5%), solid organ malignancy (25.4%), and neutropenia (31.5%). The recent use of carbapenem was seen in 56.9% of the cases in total, and more than one-third of the patients in our hospitals were treated with carbapenem at the onset of SMB. Of 28 (63.6%) of 44 cases treated for *S. maltophilia*, those who did not survive were more likely to have been treated with broad-spectrum antibiotics. A multivariate analysis revealed that a higher updated Charlson Comorbidity Index [odds ratio (95% confidence interval), 1.75 (1.11-2.75); p=0.015] and intubation [odds ratio (95% confidence interval), 12.6 (1.62-97.9); p=0.016] were associated with mortality in our cases. Pathogens were often resistant to ceftazidime but susceptible to minocycline, trimethoprim/sulfamethoxazole, and fluoroquinolones. The overall mortality rates within 30 and 90 days were 37.5% and 62.5%, respectively.

Conclusion The clinical characteristics of SMB in Japanese cases were similar to those reported from other countries. Clinicians should be aware that breakthrough infection by *S. maltophilia* may occur during administration of carbapenem.

Key words: bacteremia, breakthrough infection, carbapenem, nosocomial infection, *Stenotrophomonas maltophilia*

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Introduction

Stenotrophomonas maltophilia is an aerobic non-fermenting Gram-negative bacillus that ubiquitously inhabits the environment (1). The organism is considered the third-most frequent nosocomial pathogen among non-fermentative bacteria, following *Pseudomonas aeruginosa* and *Acinetobacter* spp. (2). *S. maltophilia* has intrinsic and acquired resistance to multiple antibiotics (3, 4) and usually infects those who are critically ill or immunocompromised (5). The mortality rate of *S. maltophilia* infection is considerably high (6, 7). In cases of bacteremia, 30-day mortality rates have been reported to range between 11% and 51% (8-14). Physicians therefore need to have a detailed knowledge of the clinical characteristics of such a fatal infection.

The clinical features of *S. maltophilia* bacteremia (SMB) in other countries have been described (14-16); however,

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those of Japanese cases have not yet been reported. To our knowledge, there have been three case series reported from Japanese medical facilities: 53 cases by Araoka et al. in 2010 (8), 54 cases by Hotta et al. in 2013 (9), and 30 cases by Sumida et al. in 2015 (10). We conducted an additional investigation of SMB in two other hospitals in Japan and summarized the data combined with these previous reports to reveal the clinical characteristics of SMB in Japanese clinical settings.

Materials and Methods

This retrospective observational study was conducted at Okayama University Hospital [OUH, which has 865 beds and 3 intensive care units (ICUs)] and Tsuyama Chuo Hospital (TCH, 535 beds and 1 ICU) in Okayama, Japan. The study period was set at January 2007 through December 2013 (7 years). The subjects were patients with positive results of *S. maltophilia* on blood culture examination, along with clinical symptoms of systemic infection. The present study was approved by the Institutional Review Boards of both OUH (No. 1504-01) and TCH (No. 172).

A medical chart review was performed for data on patients' clinical backgrounds, admission wards, time (days) from admission to the occurrence of SMB, underlying diseases, primary focus of bacteremia, results of blood culture, history of antibiotics use, and prognosis. The source of the bacteremia was clinically determined by referencing the results of microbiological examinations. The definition of neutropenia was set as an absolute peripheral blood neutrophil count of $<500/mm^3$ at the onset of bacteremia. For the history of antibiotic use, patient records were searched for the administration of carbapenem and anti-methicillin-resistant *Staphylococcus aureus* (MRSA) drugs within 30 days before the onset of SMB. When other bacteria in addition to *S. maltophilia* were detected in blood cultures, it was regarded as polymicrobial bacteremia. The 30-day and 90-day mortalities were defined as the periods from the onset of SMB to patient death. Patients who were administered carbapenem at the onset of SMB were extracted for a sub-group analysis (Carbapenem group). We compared the clinical backgrounds of survivors and non-survivors in OUH and TCH in terms of age, sex, updated Charlson Comorbidity Index (CCI) (17), Sequential Organ Failure Assessment (SOFA) score (18) at the onset of SMB, ICU admission, intubation and neutropenia.

For blood culture analysis, the BACTEC 9240 system (Becton Dickinson Microbiology Systems, Tokyo, Japan) was used at OUH, and the BacT/Alert system (Sysmex bioMérieux, Tokyo, Japan) was used at TCH. Bacterial identification and antibiotic susceptibility testing was done using automatic systems: the VITEK2 (Sysmex bioMérieux) at OUH and MicroScan WalkAway (Siemens Healthcare Diagnostics, Tokyo, Japan) at TCH. Clinical breakpoints set by the Clinical and Laboratory Standards Institute (M100-S22) were used to judge the drug susceptibility.

For the patients' characteristics, the continuous variables were summarized as the median and interquartile range. The characteristics of survivors and non-survivors were compared using the chi-squared test for categorical variables and the Mann-Whitney test for continuous variables. The risk factors for the prognosis were analyzed by stepwise logistic regression. The survival was estimated using the Kaplan-Meier method, and survival estimates were compared using the log-rank test. All p values of 0.05 or less were considered statistically significant. The statistical analyses were performed with the EZR software program, which is a modified version of R commander (The R Foundation for Statistical Computing, Vienna, Austria) (19).

Results

During the study period, 38 cases of SMB were recognized at OUH and 6 cases at TCH. A summary of all 44 cases is shown in Table 1, along with previously reported Japanese cases (8-10).

In our two hospitals, there were 28 male and 16 female patients, with a mean age of 48.9 years (range, 0-88 years). Combined with the 3 previous reports, the total number of SMB patients reached 181 (110 men and 71 women). In our hospitals, more than half of the patients were admitted to an ICU (52.3%) or intubated (54.5%). The ICU admission rate was higher in our study than in previous reports (35.2% and 36.7%) (9, 10). The mean number of hospitalization days before the occurrence of SMB were longer in our study than in a previous study; 59.7 days (6 to 145 days) in our hospitals and 50 days (28 to 100 days) in the previous study (9).

For underlying conditions, hematologic malignancy was the most common (66 cases, 36.5%), followed by solid organ malignancy (46 cases, 25.4%) and neutropenia (57 cases, 31.5%). The primary infectious site varied; central line-associated blood stream infection was the most common but it was unclear in 35.1% to 45.3% of the cases. Approximately 30% (16.2% to 37.7%) of the SMB occurred as polymicrobial bacteremia. Prior use of carbapenem and anti-MRSA drugs was seen in approximately half of the cases, ranging from 40.7% to 73.3% and 35.8% to 63.3%, respectively. The 30-day mortality rates were 34.5% in all, and the 90-day mortality at our hospitals was 45.5%.

Data on the Carbapenem group was only available at our two hospitals, where 16 (36.4%) of the 44 cases were classified into this group. Overall, the Carbapenem group shared similar clinical characteristics, such as a high ICU admission rate (56.3%) and longer hospital admission (68.5 days on average). Malignancy and neutropenia were also common as underlying diseases, and central line-associated blood stream infection was the most common focus (37.5%). The clinical characteristics and outcomes of the Carbapenem group are also summarized in Table 1.

The survivors and non-survivors for the whole hospitalized period in our hospitals are compared in Table 2. The SOFA scores were calculated in 68.2% of cases (30/44

Table 1. **Summary of Clinical Characteristics and Outcome of *Stenotrophomonas maltophilia* Bacteremia.**

	OUH + TCH (n = 44)	Araoka et al. (n = 53)	Hotta et al. (n = 54)	Sumida et al. (n = 30)	Total (n = 181)	Carbapenem group (n =16)
Study period	Jan 2007-Dec 2013	Jan 1996-Apr 2009	Jan 2005-Sep 2012	Jan 2005-Aug 2014	-	Jan 2007-Dec 2013
Age (mean)	0-88 (48.9)	19-88 (58)	39.3-65.3 (56)	n.d. (51)	-	0-73 (42.1)
Sex (M/F)	28/16	38/15	26/28	18/12	110/71	12/4
ICU admission	23 (52.3%)	n.d.	19 (35.2%)	11 (36.7%)	-	9 (56.3%)
Intubation	24 (54.5%)	n.d.	n.d.	n.d.		10 (62.5%)
Hospital days to SMB (mean)	6-145 (59.7)	n.d.	28-100 (50)	n.d.	-	1-245 (68.5)
Underlying diseases						
Hematologic malignancy	13 (29.5%)	30 (56.6%)	7 (12.9%)	15 (53.3%)	66 (36.5%)	6 (37.5%)
Solid organ malignancy	10 (22.7%)	11 (20.8%)	21 (38.9%)	4 (13.3%)	46 (25.4%)	2 (12.5%)
Neutropenia	8 (18.2%)	28 (52.8%)	8 (14.8%)	12 (40.0%)	57 (31.5%)	5 (31.3%)
Primary focus of bacteremia						
Central venous catheter	16 (36.4%)	8 (15.1%)	12 (22.2%)	22 (73.3%)	48 (26.5%)	6 (37.5%)
Respiratory	2 (4.5%)	8 (15.1%)	8 (14.8%)	n.d.	-	0
Abdominal	5 (11.4%)	12 (22.6%)	14 (25.9%)	n.d.	-	2 (12.5%)
Skin and Soft tissue	2 (4.5%)	1 (1.9%)	0	n.d.	-	1 (6.25%)
Unknown	19 (43.2%)	24 (45.3%)	19 (35.1%)	n.d.	-	4 (25%)
Polymicrobial bacteremia	16 (36.4%)	20 (37.7%)	9 (16.2%)	8 (26.7%)	53 (29.3%)	4 (25%)
History of carbapenem use	28 (63.6%)[a]	31 (58.5%)[b]	22 (40.7%)[c]	22 (73.3%)[a]	103 (56.9%)	100%
History of anti-MRSA drug use	21 (47.7%)[a]	19 (35.8%)[b]	29 (53%)[c]	19 (63.3%)[a]	88 (48.6%)	9 (56.3%)
Administration of carbapenem at just the onset of SMB	16 (36.4%)	n.d.	n.d.	n.d.	-	100%
30-day mortality	11 (25%)	27 (51%)	19 (35%)	9 (30%)	66 (34.5%)	6 (37.5%)
90-day mortality	20 (45.5%)	n.d.	n.d.	n.d.	-	10 (62.5%)

OUH: Okayama University Hospital, TCH: Tsuyama Chuo Hospital, ICU: intensive care unit, MRSA: methicillin-resistant *Staphylococcus aureus*, SMB: *Stenotrophomonas maltophilia* bacteremia, n.d.: not described

[a]within 30 days; [b]within 1 week; [c]within 2 weeks.

Patients in the Carbapenem group are defined as those who had been administered carbapenem upon their diagnosis with SMB.

Table 2. **Comparison of Survivors and Non-survivors in Our Hospitals.**

		Survivors (n=23)	Non-Survivors (n=21)	p
Age	Median (25%-75% percentile)	49 (36.5-63)	54 (28-72)	0.605[b]
Sex	Male	14	14	0.690[a]
	Female	9	7	
Updated CCI	Median (25%-75% percentile)	2 (1-2)	3 (2-5)	0.002[b]
SOFA score	Median (25%-75% percentile)	2 (1-3)	4 (3-4)	0.022[b]
ICU admission	No	15	6	0.019[a]
	Yes	8	15	
Intubation	No	15	5	0.008[a]
	Yes	8	16	
Neutropenia	No	21	15	0.126[a]
	Yes	2	6	

[a]Pearson's chi-squared test ; [b]Mann-Whitney test.

CCI: Charlson Comorbidity Index, SOFA: Sequential Organ Failure Assessment, ICU: intensive care unit, Survivors: patients those who were treated well and discharged, Non-Survivors: patients those who died in the hospitals

Calculating rate of the SOFA score was 68.2% (30/44 cases).

Table 3. **Multivariate Analysis of Clinical Characteristics on Prognosis in Our Hospitals.**

	p	odds ratio (95% C.I.)
Updated CCI	0.015	1.75 (1.11-2.75)
Intubation	0.016	12.6 (1.62-97.9)

C.I.: confidence interval

CCI: Charlson Comorbidity Index

cases); 17 survivors and 13 non-survivors. Although there were no significant differences in age, sex, or the presence of neutropenia between the two survival groups, non-survivors had significantly higher updated CCI scores (p= 0.002), SOFA scores (p=0.022), rates of ICU admissions (p= 0.019) and intubation (p=0.008) than survivors. The multivariate analysis revealed that updated CCI score (odds ratio, 1.75; 95% confidence interval: 1.11-2.75; p=0.015) and intubation (odds ratio, 12.6; 95% confidence interval: 1.62-97.9; p=0.016) were associated with a poor prognosis (Table 3).

The antibiotic susceptibilities are shown in Table 4, along with data derived from previous reports from abroad. Pathogens obtained from the SMB cases generally showed lower

Table 4. **Results of Antibiotics Susceptibility Testing for *Stenotrophomonas maltophilia*.**

[references]	OUH (n = 38)	TCH (n = 6)	[9] (n = 54)	[3] (n, unknown)	[16] (n = 102)	[15] (n = 153)
Ceftazidime	57.9%	33.3%	42.6%	15-24%	53.0%	n.d.
Ciprofloxacin	78.9%	n.p.	n.d.	16-61%	n.d.	n.d.
Levofloxacin	84.2%	66.7%	82%	n.d.	92.9%	89.8%
Minocycline	100%	100%	100%	97%	n.d.	99.4%
TMP/SMX	*75%.	100%	81.5%	75-98%	97.1%	68.9%

n.d.: not described, n.p.: not performed, TMP/SMX: trimethoprim-sulfamethoxazole
*At OUH, antibiotic susceptibility testing for TMP/SMX was performed in only 4 cases (10.5%). Susceptibility was determined on the basis of the Clinical and Laboratory Standards Institute.

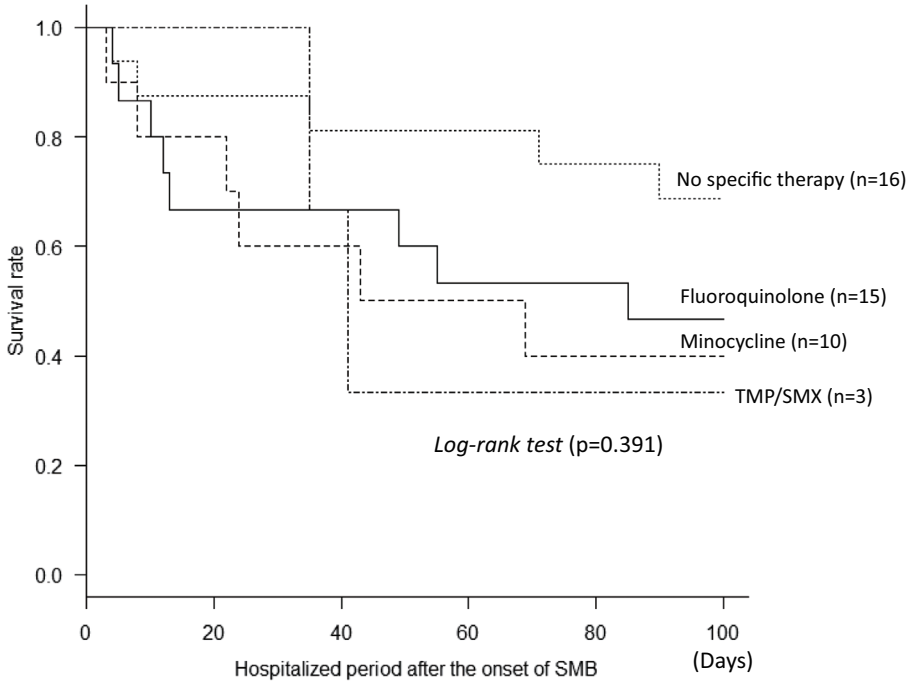

Figure. **A comparison of the prognosis with each antimicrobial therapy. The prognosis of the cases treated with fluoroquinolones, minocycline, TMP/SMX as well as 'no specific therapy' are shown with the respective Kaplan-Meier curves. TMP/SMX: trimethoprim-sulfamethoxazole**

susceptibility to ceftazidime and greater susceptibilities to fluoroquinolones, minocycline, and trimethoprim-sulfamethoxazole (TMP/SMX).

The prognoses of the cases at our hospitals are shown in Figure. Remarkably, 11 (68.8%) of 16 patients without appropriate treatment for *S. maltophilia* survived. Fluoroquinolones (ciprofloxacin, levofloxacin, and pazufloxacin) were most frequently administered (15 cases) and achieved the highest survival rate (46.7%) among all of the antibiotic therapies. There were no significant differences between each antibiotic therapy and 'no specific therapy' (p=0.391).

Discussion

We described 44 patients with SMB from our 2 medical facilities along with the 3 previously reported cases in Japan. We found that (i) the clinical characteristics of Japanese patients with SMB were similar to those reported abroad, (ii) more than one-third of the patients in our hospitals were given carbapenem upon their diagnosis with SMB, and (iii) the prognosis of the patients was associated with the underlying diseases and clinical severity but not with the administered antimicrobials.

The clinical backgrounds of Japanese SMB cases were similar to those reported abroad. As previously described (4, 16), a high ICU admission rate, longer hospital stay before SMB onset, and high comorbidity of malignancy are similarly seen in Japanese cases. Although a report from Taiwan showed that community-acquired cases accounted for 38.6% of all cases (15), they were rarely observed in our cases. The percentages of neutropenia as a comorbidity may vary in different situations; it was seen in only 5.3% of patients in one report (15) and in 25.5% in another (16). In the present study, the number of cases with neutropenia was higher, affecting 31.5% of patients on average (range, 14.8-52.8%).

The primary infectious sources for SMB in our studies did not differ markedly from previous reports (15, 16); cen-

tral line-associated blood stream infection was predominantly observed, followed by respiratory and abdominal infections. Of note, bacteremia with unknown origin was seen in 35.1% to 45.3% of the cases in our study. While this seems relatively high, the previous case series also reported similar or higher rates of SMB cases with no apparent origins (25.5 to 55.3%) (15, 16). Patients with SMB are generally in a complicated state, and determining the primary foci may be challenging.

More than one-third of the patients in our hospitals were given carbapenem upon their diagnosis with SMB. Prior use of carbapenem is included as a risk factor for *S. maltophilia* infection (3, 20-24). *S. maltophilia* is intrinsically resistant to carbapenem, and selection pressure can facilitate overgrowth of the bacterium (25). According to a previous report, carbapenem were administered in 30% (29/98 cases) of SMB cases prior to blood culture examinations (13). In the Japanese cases, although the definitions of prior use were different, the average rate of prior carbapenem use was 56.9% (range, 40.7-73.3%). Additionally, 36.4% of the patients in our hospitals were treated with carbapenem when *S. maltophilia* was isolated from their blood culture. Although the relevance of pre-use of carbapenem and the onset of SMB has been reported as above, the usage rate of carbapenem at the initial diagnosis of SMB has never been reported. Clinicians should note that a breakthrough infection by *S. maltophilia* may occur in severely ill patients being treated with carbapenem.

The prognosis of the patients was related to the predisposing underlying diseases, but not antimicrobial treatment. Interestingly, patients without specific treatment for *S. maltophilia* showed a paradoxically higher survival rate than those who received treatment, although not to a significant degree (Figure). A similar phenomenon was seen in a recent report on candidemia (26). SMB is reported to yield a worse outcome than other non-fermenting Gram-negative bacteria such as *P. aeruginosa* (10). However, our results suggested that SMB itself may not lead to fatal outcomes but can be a prognostic factor for critically ill patients.

Antibiograms were not markedly different between our isolates and previous ones (Table 4). *S. maltophilia* showed higher susceptibility rates to TMP/SMX, minocycline, and fluoroquinolones than to ceftazidime. The susceptibility to TMP/SMX, a first-line drug for *S. maltophilia* infection, is known to vary between regions. For example, almost all strains were susceptible in Korea and Switzerland, while resistant strains were frequently isolated in Turkey (15%), Taiwan (25%), and Spain (27%) (27, 28). However, the combination drug is the only known antimicrobial to which the emergence of resistance to *S. maltophilia* during the administration has not yet been reported (29). Thus, TMP/SMX is recommended as the first choice for treating *S. maltophilia* infections in Western countries (14, 27, 30, 31), still not covered by Japanese medical insurance. Although the susceptibility to TMP/SMX was evaluated in only 4 cases (10.5%) at OUH, we believe that it should be implemented at every medical laboratory when *S. maltophilia* is isolated.

The limitations of this study are its retrospective nature and the small number of cases. Nevertheless, the data shown in this study can prove valuable with the eventual accumulation of more cases. In the future, a nation-wide study should be conducted to determine the overall state of SMB in Japan.

In conclusion, we summarized a total of 181 Japanese cases of SMB, which is clinically rare but can be associated with a poor prognosis. The clinical characteristics of the Japanese cases were similar to those previously reported from abroad. Nearly 40% of the patients in our hospitals were administered carbapenem at the diagnosis of the infection. Clinicians should note that a breakthrough infection by *S. maltophilia* may occur during the administration of broad-spectrum antibiotics.

The authors state that they have no Conflict of Interest (COI).

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