Title:

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

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Abstract

Background: *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:** Medical charts of patients with SMB were retrospectively reviewed at two medical facilities (Okayama University Hospital and Tsuyama Chuo Hospital) for 7 years. The data were analyzed along with those previously reported from Japanese facilities. **Result:** A total of 181 patients (110 men and 71 women) were evaluated. 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. More than one-third of the patients in our hospitals were treated with carbapenem at the onset of SMB. While 28 (63.6%) of 44 cases were treated for *S. maltophilia*, and those who did not survive were more likely to have been treated with broad-spectrum antibiotics. Multivariate analysis demonstrated higher updated Charlson Comorbidity Index (odds ratio (OR), 1.75 [1.11-2.75]; p=0.015) and intubation (OR, 12.6 [1.62-97.9]; p=0.016) were associated with mortality in our cases. Pathogens were often resistant to ceftazidime, while susceptible to minocycline, trimethoprim/sulfamethoxazole, and fluoroquinolones. The overall mortality rates within

30 days and 90 days were 37.5% and 62.5%, respectively. **Conclusion:** 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*

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 a wide range of intrinsic and acquired resistance to multiple antibiotics (3, 4), and usually infects those who are critically ill or immunocompromised (5). Mortality rate of *S. maltophilia* infection has been 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.

Clinical features of *S. maltophilia* bacteremia (SMB) in other countries have been described (14-16); however, those of Japanese cases have not yet been uncovered. 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.

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Materials and Methods

This retrospective observational study was conducted at Okayama University Hospital (OUH, which has 865 beds including three ICUs) and Tsuyama Chuo Hospital (TCH, 535 beds including one 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 referring to the result 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

82 detected from blood cultures, it was regarded polymicrobial bacteremia. The 30-day and
83 90-day mortalities were defined as periods from the onset of SMB to patients' death.
84 Patients who were administered carbapenem at the onset of SMB were extracted for a
85 sub-group analysis (named as Carbapenem group). We compared clinical backgrounds of
86 survivors and non-survivors in OUH and TCH in terms of age, sex, updated CCI
87 (Charlson Comorbidity Index) (17), SOFA (Sequential Organ Failure Assessment) score
88 (18) at the onset of SMB, ICU admission, intubation and neutropenia.

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

96 For the patients' characteristics, continuous variables were summarized using
97 medians and interquartile range. Characteristics of survivors and non-survivors were
98 compared using chi-squared test for categorical variables and Mann-Whitney test for
99 continuous variables. Risk factors for the prognosis were analyzed by stepwise logistic

regression. Survival was estimated with Kaplan-Meier method and survival estimates were compared by using the log-rank test. All *p*-values of 0.05 or less were considered statistically significant. The statistical analyses were performed with EZR software, 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 of the 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 three 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 compared to those reported in previous reports (35.2% and 36.7%). The mean hospitalization days before the occurrence of SMB were longer; 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%) in total. The primary infectious site varied, but central line-associated blood stream infection was the most common. Notably, 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 were seen in approximately half of the cases, ranging 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 there were 16 (36.4%) of the 44 cases. Overall, the Carbapenem group showed a similar clinical characteristic; 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 outcome of the Carbapenem group are also summarized in **Table 1**.

Comparison of survivors and non-survivors for whole hospitalized period in our hospitals are shown in **Table 2**. SOFA scores were calculated in 68.2% (30/44 cases); 17 cases in survivors and 13 cases in non-survivors. Although there were no significant differences in age, sex and presence of neutropenia between the two groups, non-survivors were significantly associated with higher updated CCI score (p=0.002), SOFA score (p=0.022), ICU admission (p=0.019) and intubation (p=0.008). A result of the multivariate analysis demonstrated 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

142 interval: 1.62-97.9; p=0.016) was related with poor prognosis (**Table 3**).

143 The antibiotic susceptibility are shown in **Table 4**, with data derived from
144 previous reports from abroad. Pathogens obtained from the SMB cases generally showed
145 lower susceptibility to ceftazidime. On the other hand, the susceptibility to
146 fluoroquinolones, minocycline and trimethoprim-sulfamethoxazole were largely
147 favorable.

148 Prognosis of the cases at our hospitals is shown in **Fig. 1**. Remarkably, 11
149 (68.8%) of 16 patients without appropriate treatment for *S. maltophilia* survived.
150 Fluoroquinolones (ciprofloxacin, levofloxacin, and pazufloxacin) were most frequently
151 administered (15 cases) and achieved the highest survival rate (46.7%) among all of the
152 antibiotic therapies. There were no significant differences between each antibiotic therapy
153 and no specific therapy ($p = 0.391$).

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Discussion

We have herein summarized 44 patients with SMB from our two medical facilities along with the three previously reported cases in Japan. This report highlights 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) prognosis of the patients could be 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), high ICU admission rate, longer hospital stay before SMB onset, and high comorbidity of malignancy are similarly seen in the Japanese cases. Although a report from Taiwan showed that community-acquired cases accounted for 38.6% of all cases (15), such cases have rarely been 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 comparatively higher, affecting 31.5% of patients on average (range; 14.8 to 52.8%).

The primary infectious sources for SMB in our studies did not differ from the previous reports (15, 16); central line-associated blood stream infection was predominantly observed, followed by respiratory and abdominal infections. Remarkably, bacteremia with unknown origin was seen in 35.1 to 45.3% of the cases in our study. It seems higher proportions, but the previous case series also reported similar or higher rates of SMB cases without apparent origins (25.5 to 55.3%) (15, 16). Patients with SMB are generally in complicated states, and determining the primary foci may be relatively 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 prior to blood culture examinations (13). In the Japanese cases, although the definitive terms of prior use were different, the average rate of prior carbapenem use reached up to 56.9% (range, 40.7 to 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,

192 the usage rate of carbapenem at the initial diagnosis of SMB has never been reported.
193 Clinicians should note that a breakthrough infection by *S. maltophilia* may occur in
194 severely ill patients being treated with carbapenem.

195 Prognosis of the patients was related with predisposing underlying diseases, but
196 not antimicrobial treatment. Interestingly, patients without specific treatment for *S.*
197 *maltophilia* showed a paradoxically higher survival rate, although there was no significant
198 difference (**Fig. 1**). Similar phenomenon was seen in a recent report on candidemia (26).
199 SMB is reported to yield a worse outcome compared to other non-fermenting Gram-
200 negative bacteria such as *P. aeruginosa* (10). However, our results suggested that SMB
201 itself may not lead to fatal outcomes, but can be one of prognostic factors for critically ill
202 patients.

203 Antibiograms were not much different among our isolates and previous ones
204 (**Table 4**). *S. maltophilia* showed high susceptibility rates to TMP/SMX, minocycline and
205 fluoroquinolones, compared to ceftazidime. The susceptibility to TMP/SMX, a first line
206 drug for *S. maltophilia* infection, is known to vary between regions. For example, almost
207 all strains were susceptible in Korea and Switzerland, while resistant strains were
208 frequently isolated in Turkey (15%), Taiwan (25%), and Spain (27%) (27, 28). However,
209 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 still recommended as the first choice for treating *S. maltophilia* infections in western countries (14, 27, 30, 31), yet not been covered by Japanese medical insurance. Although the susceptibility for TMP/SMX was performed in only four 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 include its retrospective nature, and the small number of the cases. Nevertheless, the data shown in this study would be valuable owing to the accumulation of cases. In future, a nation-wide study would be needed to determine the overall picture of SMB in Japan.

In conclusion, we summarized a total of 181 Japanese cases of *S. maltophilia* bacteremia that is clinically rare but potentially associated with 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 with 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.

Declaration:

The authors state that there are no conflicts of interests to declare.

Authors' Contributions:

HE and HH drafted the manuscript. HE, HH and YH collected the clinical data. EK contributed to statistical analysis. FO edited throughout the manuscript. All authors read and approved the final manuscript.

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Figure Legends:

Fig. 1. Comparison of prognosis among each antimicrobial therapy.

Prognosis of the cases treated with fluoroquinolones, minocycline, TMP/SMX as well as no-specific therapy are shown in the Kaplan-Meier curve. TMP/SMX, trimethoprim-sulfamethoxazole.

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)

CCI, Charlson Comorbidity Index

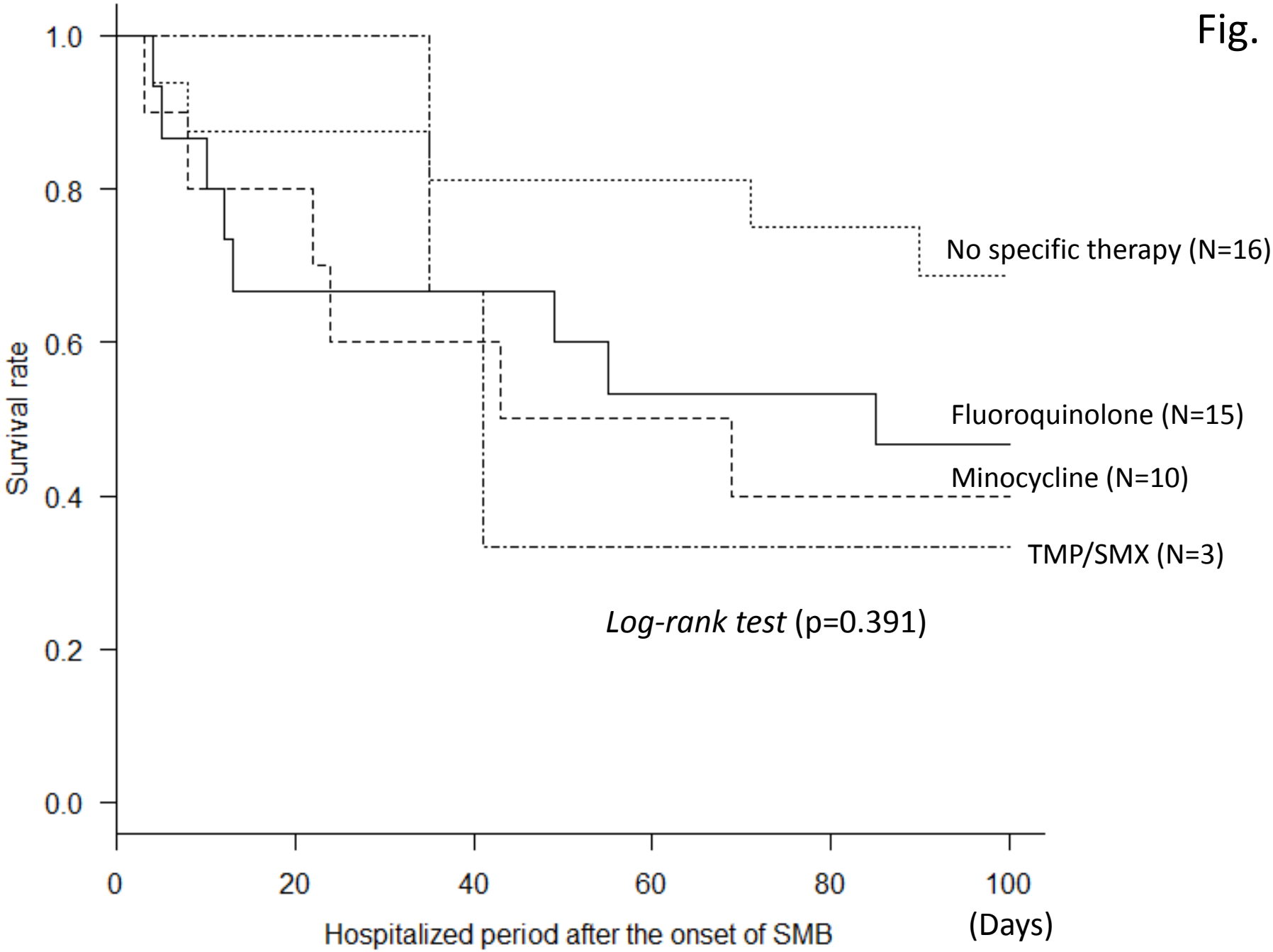
Table 4. Results of antibiotics susceptibility testing for *Stenotrophomonas maltophilia*

[references]	OUH (N = 38)	TCH (N = 6)	Hotta *et al.* [9] (N = 54)	Safdar *et al.* [3] (N, unknown)	Garazi *et al.* [16] (N = 102)	Chang *et al.* [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.

Fig. 1


1.0
0.8
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0.4
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0.0
Survival rate
0
20
40
60
80
100
(Days)
Hospitalized period after the onset of SMB
No specific therapy (N=16)
Fluoroquinolone (N=15)
Minocycline (N=10)
TMP/SMX (N=3)
Log-rank test (p=0.391)