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ORIGINAL ARTICLE

Stenotrophomonas maltophilia bloodstream infection: Comparison between community-onset and hospital-acquired infections

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KEYWORDS
Bacteremia;
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Background/Purpose: Stenotrophomonas maltophilia has been recognized as an important nosocomial pathogen, but few reports have discussed *S. maltophilia* infection in the community settings. This study aimed to reveal characteristics of patients with community-onset *S. maltophilia* bloodstream infection (SMBSI), to specify the subgroup of healthcare-

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Community;
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associated (HCA) infection in the community-onset group and to compare them with hospital-acquired (HA) SMBSI patients.
Materials and methods: Medical charts of adult patients with SMBSI presenting to a medical center in southern Taiwan from May 2008 to October 2011 were reviewed and analyzed retrospectively.
Results: Among 153 patients, we observed a high percentage (38.6%) of SMBSI to be community onset. Among community-onset SMBSI, 45.8% were community-acquired (CA) and 54.2% were HCA. The crude mortality rates were 11.1%, 18.8%, and 60.6% in the CA, HCA, and HA groups, respectively. Structural/mechanical abnormalities were observed in 32.7% of all cases, and 60% of those were related to malignancy. Independent risk factors for mortality in community-onset SMBSI were liver cirrhosis, liver metastasis, and a high Pitt bacteremia score, whereas structural/mechanical abnormalities and a high Pitt bacteremia score related to increased mortality in HA SMBSI.
Conclusion: Community-onset *S. maltophilia* infection deserves attention. Patients with community-onset SMBSI have reduced disease severity and lower mortality rate when compared to HA SMBSI. Underlying structural/mechanical abnormalities, especially those caused by malignancies, are common in SMBSI cases and should be investigated when bacteremia occurs.
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Introduction

Stenotrophomonas maltophilia, formerly named *Pseudomonas* and then *Xanthomonas maltophilia,* is a ubiquitous aerobic nonfermentative Gram-negative bacillus that exists in humid environments, water sources, soil, and plants.[1] Because of its limited pathogenicity and multidrug resistance, *S. maltophilia* is considered to be an opportunistic pathogen and an important nosocomial pathogen. Reports of it causing community-acquired (CA) infection are uncommon.[2] Risk factors for *S. maltophilia* infection include underlying malignancy, presence of indwelling devices, chronic respiratory diseases, immunocompromised status, prior use of antibiotics, and long-term stay in the hospital or intensive care unit (ICU).[1] Characteristics of community-onset *S. maltophilia* infection and its importance have not been clearly described. One recent review article focusing on CA *S. maltophilia* infections concluded that *S. maltophilia* infections are not restricted to hospitalized patients.[2] Case reports and series gave a glimpse into the various manifestations of *S. maltophilia* infections in community settings, including meningitis, endocarditis, wound and soft-tissue infection, bacteremia, sinusitis, osteochondritis, chronic enteritis, and other conditions.[2] However, to our knowledge, no study has offered a comprehensive perspective on community-onset *S. maltophilia* infections. This retrospective study aimed to elucidate the patient demographics and clinical features of community-onset *S. maltophilia* bloodstream infection (SMBSI). In addition, we used clear definitions of CA, healthcare-associated (HCA), and hospital-acquired (HA) infections, and compared the differences and risk factors for mortality between these specific patient groups.

Materials and methods

Settings and study design

This retrospective study was conducted in a 1700-bed tertiary hospital in southern Taiwan from May 2008 to October 2011. The study population enrolled adult patients, aged $\geq$18 years, with *S. maltophilia* bacteremia. Medical charts were reviewed and all data were recorded under the approval of the hospital's Institutional Review Board. Only the clinical characteristics of the first episode of bacteremia were analyzed for each patient.

Definitions

Bloodstream infection is defined as the isolation of bacteria from one or more peripheral venous blood samples collected from a patient associated with the symptoms and signs relevant to systemic infection. The probable source (including respiratory, urinary, gastrointestinal, skin and soft tissue, bone, and joint) was determined by microbiological results and physicians' clinical interpretations according to Centers for Disease Control (CDC) definitions.[3] Catheter-related bloodstream infections were defined according to the management guidelines of the Infectious Diseases Society of America, if there was no apparent source for the bacteremia except the central venous catheter (CVC) and when the organism was isolated in a positive semiquantitative culture ($>$15 CFU) from the CVC tip with a positive peripheral blood culture for the same organism.[4] Hospital-acquired bloodstream infection (HABSI) was defined by a positive blood culture obtained from patients who were hospitalized for $>$48 hours. Community-onset bloodstream infection (COBSI) was defined by a positive blood culture obtained from patients who were either not hospitalized or hospitalized for $\leq$48 hours.

The community-onset group was further divided into HCA and CA subgroups. The relationship among the three subgroups is presented in Fig. 1. COBSI was defined by a positive blood culture drawn within 48 hours after hospitalization for patients who did not attend any healthcare facilities in 90 days or reside in nursing home.[5–7] Episodes were considered HCA according to the definition of Friedman et al,[5] if the patient fulfilled any of the following criteria: (1) received intravenous therapy at home, received

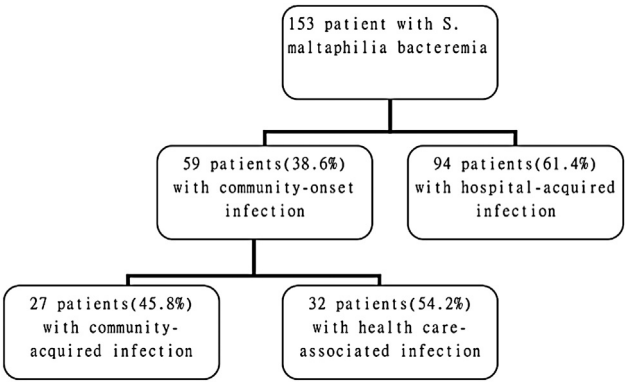

Figure 1. Relationship among patient subgroups.

wound care or specialized nursing care, or self-administered intravenous medical therapy in the 30 days before the bloodstream infection; (2) attended a hospital or hemodialysis clinic or received intravenous chemotherapy within 30 days before the bloodstream infection; (3) was hospitalized in an acute care hospital for 2 or more days within 90 days before the bloodstream infection; or (4) resided in a nursing home or long-term care facility. Polymicrobial bacteremia was defined as the presence of one or more microorganism other than *S. maltophilia* in the same blood culture. A previous chemotherapy, surgery, or invasive procedure (including percutaneous transhepatic gallbladder drainage, percutaneous abscess drainage, and percutaneous nephrostomy) was recorded only when performed within 3 months of the SMBSI. Steroid therapy was defined as the use of more than 30 mg daily or an equivalent dose of prednisolone for more than 7 days before the bloodstream infection. Neutropenia was defined as an absolute neutrophil count of $<500/mm^3$ at the onset of bacteremia. Appropriate antimicrobial treatment refers to the administration of an adequate dose of an *in vitro* susceptible antibiotic within 72 hours after the blood culture was obtained and for more than 7 days. Structural or mechanical abnormality was recorded when there was documented imaging or endoscopic evidence of gastrointestinal, hepatopancreatobiliary, and urinary tract anomalies including liver metastases, pancreatobiliary tract or urinary system dilatation/obstruction,[8,9] fistulas, mechanical ileus, or severe mucositis/enteritis caused by chemotherapy, infection, or inflammatory bowel disease.[10]

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Blood cultures were incubated with BacT/Alert system (Organon Teknika, Massachusetts, USA). Species and antimicrobial susceptibility were determined using VITEK-2 (bioMerieux, Inc., Saint Louis County, Missouri, USA). Susceptibility testing results were interpreted according to the Clinical and Laboratory Standards Institute guidelines, 2010.[11]

Statistical analysis

All data were analyzed using the Statistical Package for Social Sciences (SPSS) version 18.0 (SPSS Inc., Chicago, IL, USA). Values were expressed as the mean $\pm$ standard deviation (continuous variables) or percentages of the group (categorical variables). Continuous variables were compared using Student *t* test. Categorical variables were evaluated with the chi-squared test or Fisher's exact test, as appropriate. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Two-tailed tests were used and $p < 0.05$ was considered significant. Variables with $p < 0.1$ in univariate testing were incorporated into a forward, stepwise multivariate logistic regression model to identify independent predictors for mortality.

Results

From May 2008 to October 2011, 167 episodes of *S. maltophilia* bacteremia were identified in 153 patients after the exclusion of five patients under the age of 18 years. The study population was divided into three groups: CA, HCA, and HA. These three groups comprised 17.6% ($n = 27$), 21% ($n = 32$), and 61.4% ($n = 94$) of the patients, respectively. Demographic and clinical characteristics of the patients are shown in Table 1. There were no differences in age, sex, and body mass index among the three groups. Both the HCA and the HA groups had higher percentages of underlying malignant disease than the CA group (59.4% vs. 14.8%, $p < 0.001$; 41.5% vs. 14.8%, $p = 0.003$ respectively).

Among patients with malignancy ($n = 62$), 10 had hematologic malignancy, 52 had solid tumors, and one had both. The three most common solid tumors were gastrointestinal tumors ($n = 23$, 44.2%), followed by head and neck tumors ($n = 10$, 19.2%) and hepatopancreatobiliary tumors ($n = 9$, 17.3%). There were five patients with newly diagnosed or suspected malignancy at the time of bacteremia. Among them, four had hepatopancreatobiliary tumors and one had urothelial carcinoma, all causing obstructive biliary tract infection or obstructive nephropathy. We observed more liver metastases in cancer patients with community-onset *S. maltophilia* bacteremia (CA group: 25%, HCA group: 36.8%) when compared with the HA group (15.4%). The HCA group had similar clinical conditions to those of the HA group regarding previous chemotherapy, surgery, and invasive procedures. Most of the surgeries performed were gastrointestinal (44%) and cardiovascular (32%). There were significantly longer length of ICU stay, higher crude mortality and 14-day mortality, and more episodes of polymicrobial bacteremia in the HA group. *Candidemia* constituted the highest percentage of polymicrobial episodes (19.2%), followed by coagulase-negative staphylococci (15.4%) and methicillin-resistant *Staphylococcus aureus* (15.4%). The average number of hospitalized days before SMBSI was 35.1. The HCA group had the highest Charlson Comorbidity Index, but the HA group had the highest Pitt bacteremia score (PBS). The HCA and HA groups had higher prevalence rates of catheter-related bloodstream infection (18.8% and 20.2%) and infections of unknown source (31.1% and 55.3%).

We found that the most frequent infection sources in the CA group were respiratory tract infection (12/27, 44.4%), followed by gastrointestinal (5/27, 18.5%) and urinary tract infection (4/27, 14.8%). Among the five patients with a gastrointestinal source of infection, two patients had

Table 1 Comparison of demographic and clinical characteristics of patients suffering from community-onset and hospital-acquired *S. maltophilia* bacteremia ($n = 153$)

Parameters	CO ($n = 59$)			*p*		
	CA ($n = 27$)	HCA ($n = 32$)	HA ($n = 94$)			
	n (%)	*n* (%)	*n* (%)	CA vs. HCA	HCA vs. HA	CA vs. HA
Age	57.9 (±20.4)	66.0 (±14.2)	65.2 (±16.0)	0.079	0.795	0.053
≥75	7 (25.9)	9 (28.1)	34 (36.2)	0.850	0.407	0.322
Sex						
Male	12 (44.4)	18 (56.3)	50 (53.2)	0.366	0.764	0.423
Body weight	57.5 (±13.8)	55.5 (±11.6)	58.6 (±13.4)	0.582	0.258	0.724
BMI	22.6 (±4.4)	22.2 (±4.1)	22.6 (±4.5)	0.703	0.681	0.946
Underlying diseases						
Malignancy	4 (14.8)	19 (59.4)	39 (41.5)	<0.001	0.080	0.003
Hematologic	0 (0.0)	2 (6.3)	8 (8.5)	0.495	1.000	0.197
Solid tumor	4 (14.8)	17 (53.1)	31 (33)	0.003	0.043	0.091
Hypertension	10 (37.0)	13 (40.6)	47 (50.0)	0.778	0.359	0.234
Diabetes mellitus	6 (22.2)	15 (46.9)	31 (33.0)	0.049	0.158	0.285
COPD	2 (7.4)	4 (12.5)	8 (8.5)	0.678	0.499	1.000
Chronic heart failure	3 (11.1)	6 (18.8)	10 (10.6)	0.488	0.234	1.000
Chronic renal failure	3 (11.1)	9 (28.1)	25 (26.6)	0.193	0.866	0.122
Liver cirrhosis	2 (7.4)	4 (12.5)	15 (16.0)	0.678	0.779	0.356
Liver metastases[a]	1 (25)	7 (36.8)	6 (15.4)	1.000	0.013	0.421
CCI	1.89 (±2.2)	5.68 (±2.7)	3.89 (±2.9)	<0.001	0.003	0.001
Clinical conditions						
Corticosteroid use	0 (0.0)	0 (0.0)	13 (14.0)		0.038	0.039
Chemotherapy	0 (0.0)	7 (23.3)	16 (17.0)	0.011	0.539	0.021
Appropriate antibiotics	8 (29.6)	13 (40.6)	63 (67.0)	0.380	0.008	0.001
Neutropenia	0 (0.0)	3 (9.4)	5 (5.3)	0.243	0.418	0.586
Tracheostomy	0 (0.0)	3 (9.4)	14 (14.9)	0.243	0.557	0.038
S/M abnormalities	6 (22.2)	13 (40.6)	31 (33)	0.132	0.433	0.285
Surgery[b]	0 (0.0)	13 (40.6)	37 (39.4)	<0.001	0.900	<0.001
GS	0 (0.0)	6 (46.2)	16 (43.2)	0.024	0.710	0.012
CVS	0 (0.0)	4 (30.8)	12 (32.4)	0.112	1.000	0.067
Polymicrobial	1 (3.7)	1 (3.1)	21 (22.3)	1.000	0.014	0.025
Crude mortality	3 (11.1)	6 (18.8)	57 (60.6)	0.488	<0.001	<0.001
14-d mortality	2 (7.4)	4 (12.5)	36 (38.3)	0.678	0.008	0.002
LOS	9.0 (±12.1)	15.3 (±12.5)	60.2 (±72.9)	0.056	0.001	<0.001
ICU LOS	1.52 (±7.1)	2.25 (±6.8)	19.7 (±20.2)	0.688	<0.001	<0.001
PBS	0.41 (±1.2)	1.97 (±3.6)	4.1 (±3.8)	0.027	0.007	<0.001
Source of bacteremia						
Respiratory	12 (44.4)	4 (12.5)	14 (14.9)	0.008	1.000	0.001
Urinary	4 (14.8)	4 (12.5)	1 (1.1)	1.000	0.015	0.009
Gastrointestinal	5 (18.5)	5 (15.6)	7 (7.4)	0.768	0.173	0.09
Skin and soft tissue	1 (3.7)	3 (9.4)	1 (1.1)	0.617	0.050	0.398
Osteomyelitis	1 (3.7)	0 (0)	0 (0)	0.458		0.225
Catheter related	0 (0.0)	6 (18.8)	19 (20.2)	0.027	0.858	0.007
Pelvic inflammatory disease	1 (3.7)	0 (0)	0 (0)		0.458	
Unknown source	3 (11.1)	10 (31.1)	52 (55.3)	0.113	0.019	<0.001

[a] Percentage among cancer patients.

[b] Including invasive procedures as previously defined in the text. The GS and CVS percentages refer to the ratio within the patients who underwent surgery or invasive procedures.

BMI = body mass index; CA = community acquired; CCI = Charlson Comorbidity Index; CO = community onset; COPD = chronic obstructive pulmonary disease; CVC = central venous catheter; CVS = cardiovascular surgery; GS = gastrointestinal surgery; HA = hospital acquired; HCA = healthcare associated; IAD = intra-abdominal drainage; ICU = intensive care unit; LOS = length of stay; PBS = Pitt bacteremia score; S/M abnormalities = structural/mechanical abnormalities.

biliary tract infection with biliary tract dilatation due to suspected periampullary space-occupying lesions and newly diagnosed pancreatic tumors, respectively. The other three patients had pancreatitis, adhesion ileus, and enteritis. Less common infection sources in the CA group included cellulitis (one patient), osteomyelitis (one patient), pelvic inflammatory disease (one patient), and no definite infection source (four patients).

In vitro antimicrobial susceptibilities of *S. maltophilia* to trimethoprim/sulfamethoxazole (TMP/SMX), levofloxacin, and minocycline were 68.9% (115/167), 89.8% (150/167), and 99.4% (166/167), respectively. Fig. 2 shows the antimicrobial susceptibilities in the three subgroups of CA, HCA, and HA SMBSI. They all had high susceptibility to minocycline and levofloxacin, and the CA group had the lowest susceptibility to TMP/SMX. We analyzed the annual antimicrobial susceptibility rate and found significantly increasing TMP/SMX susceptibility during the study period in the CA ($p = 0.046$) and HCA ($p = 0.013$) groups. Increasing susceptibility was not observed with levofloxacin or minocycline. The annual TMP/SMX susceptibility rate is depicted in Fig. 3.

Because the HCA group showed a lower mortality rate similar to the CA group, we performed the analysis of mortality risk factors in the two subgroups of COBSI and HABSI. Univariate analysis identified several risk factors for mortality in both COBSI and HABSI (Table 2). In the multivariate analysis (Table 2), liver cirrhosis, liver metastases, and high PBS were identified as independent risk factors for mortality in the COBSI group, whereas structural/mechanical abnormalities and high PBS were shown to be significant in the HABSI group.

Discussion

S. maltophilia has been recognized as an important opportunistic nosocomial pathogen. However, its importance in community-onset infection is seldom stressed. This study is, to our knowledge, the first retrospective study in the English-language literature to compare the demographic characteristics, clinical parameters, and mortality risk factors between community-onset and HA SMBSI and to emphasize the specific group of HCA SMBSI.

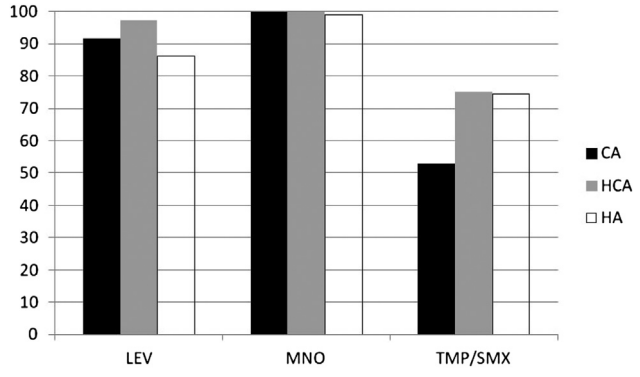

Figure 2. Antimicrobial susceptibilities in the three subgroups. CA = community acquired; HCA = healthcare associated; HA = hospital acquired; LEV = levofloxacin; MNO = minocycline; TMP/SMX = trimethoprim/sulfamethoxazole.

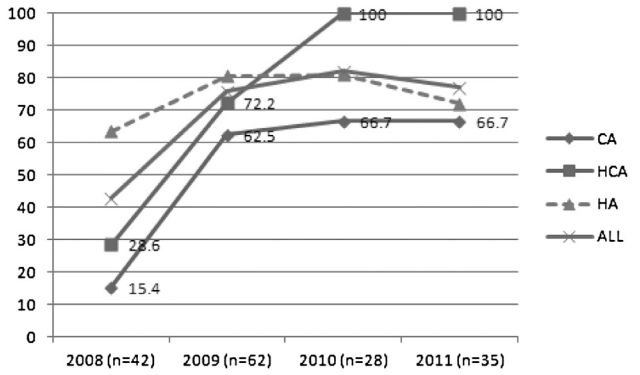

Figure 3. Yearly susceptibility to TMP/SMX overall and among the three groups. CA = community acquired; HCA = healthcare associated; HA = hospital acquired; TMP/SMX = trimethoprim/sulfamethoxazole.

We observed a relatively high percentage (38.6%) of SMBSI to be community onset when compared to the 8–24% mentioned in previous studies.[2,12–18] Falagas et al[2] proposed, as a limitation in their review, that the definition of CA infection lacked clarity. When we used clear definitions to document CA and HCA infections,[5] we found that community-onset infections were increasing and CA infections were underestimated.

Similar to a recently published study on SMBSI by Garazi et al,[17] the present study also enrolled a broad spectrum of patient population and represents the largest series of SMBSI, whereas most of the previous studies involved either a much smaller number of cases or patients with a predominant enrollment from cancer hospitals.[17] Garazi et al divided the infections into nosocomial (77.5%, $n = 79$), HCA (20.6%, $n = 21$), and CA (2.0%, $n = 2$) without any comparison between the three groups. Although their definition of HCA infection was not exactly identical to our study, we observed a similar HCA ratio and a much higher percentage of CA SMBSI.

Previous studies seldom described CA *S. maltophilia* infections in detail, and there was significant heterogeneity in patient populations. Falagas et al[2] concluded that the majority of patients with CA *S. maltophilia* infections had some kind of comorbidity, and it was difficult to infer about the outcomes in these infections.[2] In our observation, we found that there was no significant difference regarding underlying comorbidities when compared to the other two groups, except for lower prevalence of malignancy. Mortality rate was lowest among the three groups, even though only 29.6% of the patients were prescribed appropriate antibiotics.

Despite hematologic malignancy (34–57%) and neutropenia (23–53%), both being reported as common coexisting conditions in SMBSI,[13,15,19] we found an exceptionally low prevalence of hematologic malignancy and neutropenia in the present study. On the contrary, one-third of the patients had solid tumors, similar to the findings of previous reports (9–37%).

We also noted that 32.7% of our patients had documented structural/mechanical abnormalities (Table 1), 60% of which were directly related to malignancy. We hypothesize that the bacteremia could be a result of bacterial

Table 2 Univariate and multivariate analyses of risk factors associated with mortality in patients with *S. maltophilia* bacteremia

Risk factor	Community onset ($n = 59$)		Hospital acquired ($n = 94$)	
	OR (95% CI)	Adjusted OR (95% CI)	OR (95% CI)	Adjusted OR (95% CI)
Patient profiles				
Age	0.483 (0.97−1.06)		1.031 (0.99−1.04)	
Male	10.182 (1.18−87.63)		0.548 (0.24−1.27)	
Medical conditions				
Cancer	1.422 (0.34−5.98)		0.888 (0.38−2.05)	
Liver cirrhosis	7.833 (1.28−47.96)	14.923 (0.99−222.92)[a]	0.969 (0.31−2.99)	
Liver metastases	4.5 (0.851−23.80)	23.098 (1.89−281.86)[a]	0.630 (0.12−3.30)	
CCI	1.418 (1.08−1.86)		1.069 (0.922−1.24)	
S/M abnormalities	1.867 (0.44−7.94)		3.117 (1.17−8.28)	4.064 (1.41−11.69)[a]
Polymicrobial	6.125 (0.35−108.11)		1.395 (0.50−3.87)	
Unknown infection source	6.562 (1.44−29.91)		2.713 (1.16−6.36)	
Interventions				
Chemotherapy	NA		0.318 (0.10−0.97)	
Appropriate antibiotics	0.466 (0.09−2.48)		1.174 (0.49−2.82)	
Severity score				
PBS	1.47 (1.12−1.94)	1.784 (1.15−2.78)[a]	1.247 (1.08−1.44)	1.279 (1.11−1.48)[a]

[a] Significant in multivariate analysis.
NA = not available; OR = odds ratio; CI = confidence interval; CCI = Charlson Comorbidity Index; PBS = Pitt bacteremia score.

overgrowth due to certain obstructive lesions and of mucosal disruption and barrier defects caused by tumor invasion. Although colonization of *S. maltophilia* and its relationship to infection were not clearly demonstrated, our observation is in accord with the findings from previous reports in which structural anomalies were identified, in most of the cases, with biliary and urinary tract *S. maltophilia* infection.[9,14,20−23] Besides, structural/mechanical abnormalities correlated to increased mortality in the HA group. We believe that investigating possibly obstructive lesions and performing drainage or debridement may be of value in respect of treatment.

Previous literature has reported a wide range in crude mortality (21−69%) associated with SMBSI.[19,24] An attributable mortality of 26−37.5% has been reported.[25,26] In this study, we found that the crude mortality rates in the community-onset group were significantly lower than in the HA group. We also found the HCA group to be a unique category to have milder disease conditions and better outcomes than the HA group, despite having higher comorbidity scores. Thrombocytopenia, shock,[13] neutropenia, polymicrobial bacteremia with enterococci,[19] ICU stay, CVC use, and mechanical ventilation[12] were all reported as risk factors associated with mortality in *S. maltophilia* bacteremia. Multivariate analysis indicated liver cirrhosis and liver metastases to be independent risk factors for mortality in the COBSI group but not in the HABSI group. This finding implies that the underlying hepatobiliary comorbidities may be of more predictive value for mortality in COBSI than in HABSI. There is still controversy about whether administration of inappropriate antibiotics relates to increased mortality in current reports,[17] and we found no correlations between appropriate antibiotics use and mortality.

S. maltophilia is renowned for its intrinsic resistance to various antimicrobial agents, and TMP/SMX is considered to be the drug of choice.[27] However, resistance rates to TMP/SMX are highly variable in different regions, with a general susceptibility over 80%, except for high resistance reported in Taiwan (25%), Spain (27%), and Turkey (15%).[27,28] In recent studies conducted at various medical centers in Taiwan examining *S. maltophilia* infections and antimicrobial susceptibility, susceptibility to TMP/SMX ranges from 14.3% to 91%.[12,13,29−34] Most of the study populations had nosocomial infections. Only two studies mentioned an increasing resistance trend against TMP/SMX, which differed from our observation.[13,32] We observed a statistically significant increasing susceptibility to TMP/SMX in isolates from the community-onset group during 2008−2011, but not in the HA group (Fig. 3). The mechanism is not clear from the current data. The high susceptibility to minocycline during our study period is similar to the observations of a 10-year multicenter retrospective study in Taiwan; however, we did not see increasing resistance to levofloxacin.[34]

The retrospective nature of this study is its major limitation. We also had a polymicrobial bacteremia rate of 22.3% in the HABSI group, which makes it difficult to assess the influence of SMBSI on mortality. The number of patients who died in the CABSI group was too small for analysis. Risk factors for mortality among the CA, HCA, and HA SMBSI groups could be analyzed separately to better distinguish between the three groups when more cases are available.

This study is the first attempt to describe the differences between CA, HCA, and HA SMBSI groups. We suggest that *S. maltophilia* not only causes HA infections but also emerges as a pathogen in community settings. Although community-onset SMBSI was represented with lower

mortality, the observation should be emphasized due to the limited antimicrobial options for *S. maltophilia*. Liver cirrhosis and liver metastases were found as predictors of a higher mortality among *S. maltophilia* COBSI patients. Underlying structural/mechanical abnormalities should be investigated when *S. maltophilia* bacteremia is confirmed, especially in patients with malignancy.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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