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A 20-year trend of prevalence and susceptibility to trimethoprim/sulfamethoxazole of *Stenotrophomonas maltophilia* in a single secondary care hospital in Korea

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Abstract

Stenotrophomonas maltophilia is a Gram-negative opportunistic pathogen that can cause serious infection. We aimed to analyze the prevalence and susceptibility rates to trimethoprim/sulfamethoxazole of *S. maltophilia*. We conducted a retrospective study of *S. maltophilia* isolates from a university hospital from 2001 to 2020. Clinical information, the numbers of isolates and susceptibility rates were analyzed by year. Susceptibility rates and changes in respiratory and non-respiratory samples were compared. 1805 *S. maltophilia* isolates were identified, of which 81.4% (1469/1805) were from respiratory samples. There was a male predominance and 52% of the isolates were from general wards. The average susceptibility rate was 87.7% and there was no significant annual trend ($P = .519$). The susceptibility rate was 88.7% in respiratory samples and 84.1% in non-respiratory samples ($P = .018$). Susceptibility analyses using clinical data over long periods can guide the choice of antimicrobials especially for pathogen whose treatment options are limited.

Abbreviations: MIC = minimal inhibitory concentration, TMP/SMX = trimethoprim/sulfamethoxazole.

Keywords: antimicrobials, epidemiology, *Stenotrophomonas maltophilia*, susceptibility, trend, trimethoprim/sulfamethoxazole

1. Introduction

Stenotrophomonas maltophilia is a Gram-negative, obligate aerobic, non-fermentative, ubiquitous bacillus.[1] It was first isolated as *Bacterium bookeri* in 1943 and later named *Pseudomonas maltophilia* in 1963 by Hugh et al,[2] *Xanthomonas maltophilia* in 1983 by Swings et al using rRNA cistron analysis,[3] and then *S. maltophilia* in 1993 (the current name) by Palleroni and Bradbury.[4] *S. maltophilia* can cause various human infections, including pneumonia, bacteremia, soft tissue infection, osteomyelitis, meningitis, keratitis, endocarditis, and urinary tract infection.[5] This pathogen causes high morbidity and mortality in immunocompromised patients with HIV infection, malignancy, and cystic fibrosis, especially as a hospital-acquired pathogen.[6] Trimethoprim/sulfamethoxazole (TMP/SMX) is the treatment of choice for *S. maltophilia* infections.[7] Recently, there are many treatment options and some infections caused by *S. maltophilia* are treated by combination of TMP/SMX and fluoroquinolone.[5] Ticarcillin-clavulanate has been used as an alternative therapy to TMP/SMX because of the emergence of resistance to TMP/SMX.[5] Combination therapies using tigecycline and TMP/SMX, tigecycline and amikacin, and other combinations of antimicrobial agents have been also proposed and used for treatment of *S. maltophilia* infection.[5] *S. maltophilia* shows intrinsic resistance to various antibiotics, including β-lactams, aminoglycosides, fosfomycin, tetracycline, and meropenem,[8] which makes treatment difficult for clinicians. Therefore, TMP/SMX is still very important and critical drug for treatment of infecfion caused by *S. maltophilia*. Recent data from other countries show *S. maltophilia* being emerged as an important nosocomial pathogen. Moreover, several studies reported that *S. maltophilia* has increasing resistance to TMP/SMX,[5,9,10] making it difficult to determine the best antibiotics to control hospital-acquired infection, including 2 Korean studies.[11,12] Here, we analyzed trends in the susceptibility of *S. maltophilia* to TMP/SMX over the past 20 years. Because the majority of *S. maltophilia* is isolated from respiratory samples, we also compared respiratory samples with other sample types.

2. Materials and methods

2.1. Study design and data collection

This retrospective study was conducted in a 642-bed university-affiliated hospital from January 2001 to December 2020.

The authors have no funding and conflicts of interest to disclose.

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

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This hospital is located in Ilsan, Gyeonggi Province, South Korea. *S. maltophilia* from clinical isolates was included. *S. maltophilia* isolates from non-duplicate clinical samples were retrospectively acquired from the laboratory records complied during the study period. Identification and antimicrobial susceptibility testing were performed with the Vitek 2 automated identification and antimicrobial susceptibility system (bioMérieux, Marcy-L'Étoile, France) as described in the Clinical and Laboratory Standards Institute (CLSI) M100 guidelines.[8] The date of sample reception, sample type, and minimal inhibitory concentration (MIC) data for TMP/SMX of *S. maltophilia*-positive samples were acquired. The institutional review board of Inje University Ilsan Paik Hospital approved this study (IRB number: ISPAIK NON2021-002) and waived the need for informed consent because the study did not use any human tissue samples. The study was performed according to the principles of the Declaration of Helsinki.

2.2. Susceptibility analysis

Susceptibility rate and sample type were analyzed by year using Microsoft Excel 2013 (Microsoft Corp., Redmond, WA) and WHONET 5.6 (available from http://whonet.org/software.html). Microbiology positive results were collected from the laboratory information system, and then only those corresponding to *S. maltophilia* were sorted. Identification and susceptibility test were performed by automated system and susceptibility criteria for the MIC of TMP/SMX were in accordance with CLSI guideline M100.[8] According to CLSI, isolates are susceptible when MIC to TMP/SMX are 2/38 or less, and resistant when MIC to TMP/SMX are 4/76 or more.[8] The number of isolates, susceptibility rate, and sample types during the study period were analyzed, and annual trends in the susceptibility rate were calculated.

2.3. Comparison between respiratory and non-respiratory groups

The clinical specimens were divided into respiratory and non-respiratory groups to compare the susceptibility rate. Respiratory samples included sputum, bronchial or tracheal aspirates, and pleural fluid. For sputum samples, isolates grown only in grade 4 or 5 were identified and undergone antimicrobial susceptibility test. The remaining sample types were grouped as non-respiratory samples, including urine, blood, pus, catheter, bile, body fluid, skin, tissue, and wound swabs. The number of isolates and susceptibility rate, for the entire period and for each year, were calculated; those for respiratory and non-respiratory samples were then compared.

2.4. Statistical analysis

SPSS for Windows (ver. 25.0; IBM Corp., Armonk, NY) was used for all statistical analyses. Categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were analyzed using an independent sample *t* test or the Mann–Whitney *U* test. For trend analysis of susceptibility rates during the study period, the linear by linear association test was used. A 2-tailed *P* value < .05 was considered significant.

3. Results

3.1. Prevalence of S. maltophilia

During the 20-year period, 1805 *S. maltophilia* isolates were identified. The mean number of isolates was 90.15 ± 24.4/year (range: 49–138/year). The highest number of *S. maltophilia* specimens in a single year was 137, in 2015, and the lowest number was 50, in 2002. The number of isolates per year was < 100 between 2001 and 2012, but has exceeded 100 cases per year since 2013 (Fig. 1). Overall, 81.4% of the isolates (1469/1805) were from respiratory samples and 18.6% (336/1805) were from non-respiratory samples (Fig. 2). The most common respiratory tract sample type was sputum (93.9 %, 1379/1469), while the most common non-respiratory sample was urine (29.5%, 99/336), followed by blood (25.6%, 86/336), pus (15.2%, 51/336), and catheter tip (10.4%, 35/336) (Fig. 2).

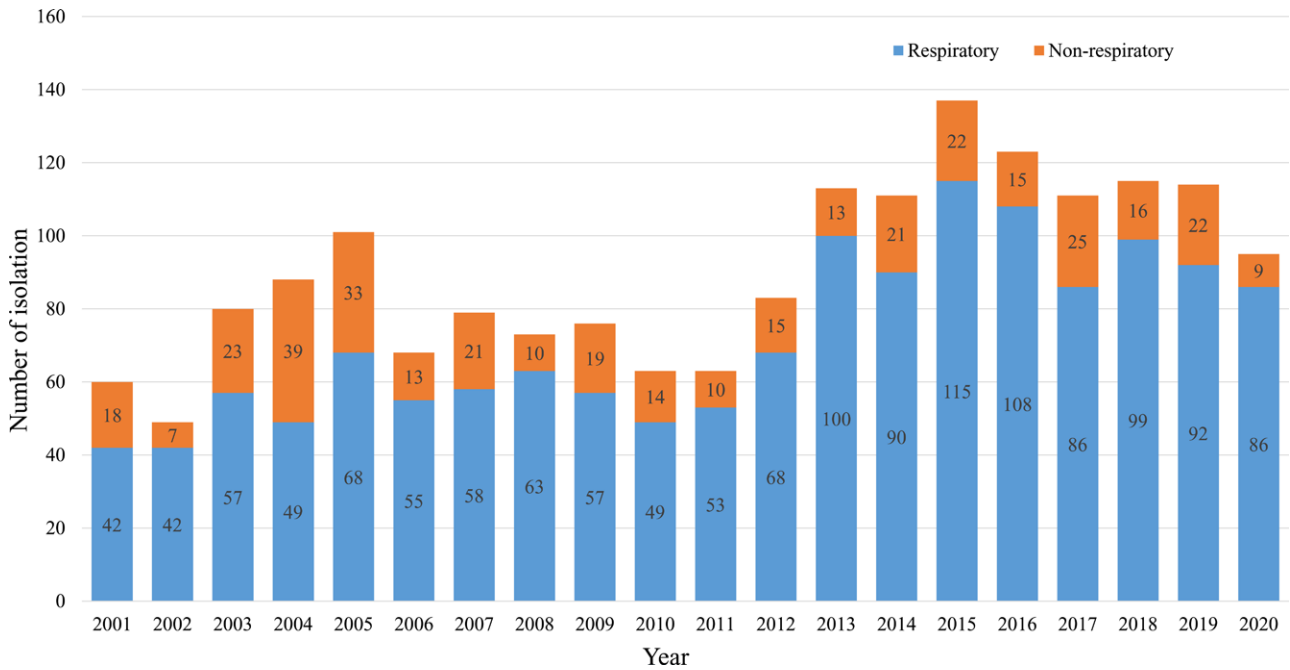

Figure 1. Number of isolates per year and origin of isolates from 2001 to 2020.

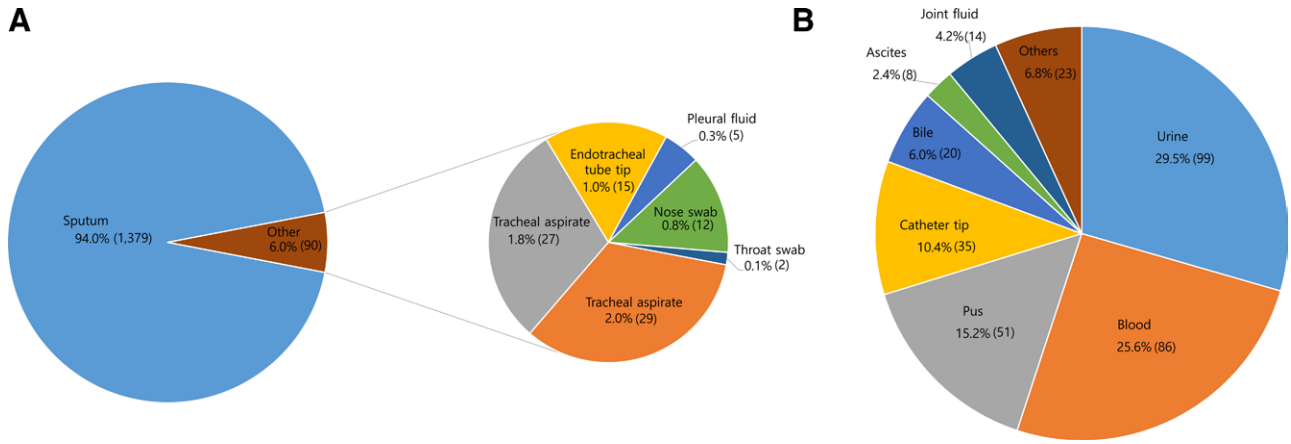

Figure 2. Composition of (A) respiratory and (B) non-respiratory *Stenotrophomonas maltophilia* samples.

3.2. Comparison of S. maltophilia isolated from respiratory and non-respiratory samples

There was no significant difference in gender ratio between the 2 groups. There was a higher proportion of men than of women (1205 [66.8%] vs 600 [33.2%]) in both groups. The mean patient age was 65.02 ± 21.01 years; it was significantly higher in the respiratory group (67.72 ± 19.03 vs 53.24 ± 24.86 years) (Table 1). At the time of isolation, patients were most likely to be admitted to a general ward (52% [938/1805]: 52.1% [766/1469] and 51.2% [172/336] from the respiratory and non-respiratory groups, respectively). At the time of isolation, significantly more patients in the intensive care unit were in the respiratory group (41.6% [611/1469] vs 20.8% [71/336]) (Table 1).

3.3. Susceptibility of S. maltophilia to trimethoprim/sulfamethoxazole

During the 20-year period, 88.7% of respiratory *S. maltophilia* were susceptible to TMP/SMX, while non-respiratory isolates were somewhat less susceptible (84.1%) (P = .018) (Fig. 3). The change in susceptibility percentage over time was significant (P = .033), which were 95.0% in 2001 and 84.2% in 2020. The direction of the change was not clear. There were no significant changes in susceptibility rate by year for respiratory samples, including in trend analysis (P = .100 and P = .075, respectively). For non-respiratory samples, there was a significant change in susceptibility rate by year (P = .003), although not in trend analysis (P = .318) (Fig. 3).

4. Discussion

This study analyzed 1805 *S. maltophilia* samples collected over a 20-year period, including 336 non-respiratory samples. This is the largest number of *S. maltophilia* non-respiratory samples to be analyzed in a susceptibility study to date. There are few studies of the prevalence, clinical characteristics, or susceptibility of *S. maltophilia* to TMP/SMX. A Hungarian study identified 160 isolates over 3 years,[13] whereas in this study the average number of isolates per year was 90. Several studies have reported a male predominance (56.3%–66.3%),[14–17] as in our study (66.8%, 1205/1805). Another Hungarian study, conducted in a 1820-bed hospital, identified 579 (58%) isolates in respiratory samples over 10 years.[18] We collected 1469 (81.4%) respiratory samples over 20 years. The results may differ according to hospital size, country, and study design.

The number of isolates showed increasing trend through 2001 to 2020 (Fig. 1). It is in the same context as other previous studies that showed *S. maltophilia* has a risk as an important pathogen in the nosocomial infection.[5] In the environment of university hospital, where there are inevitably many risk factors for *S. maltophilia* infection including underlying malignancy, presence of indwelling devices, chronic respiratory diseases, and immunocompromised hosts,[5] we should look more carefully at infections caused by *S. maltophilia*.

In this study, the overall susceptibility rate of *S. maltophilia* over 20 years was 87.7%. The reported susceptibility rate of *S. maltophilia* to TMP/SMX varies from 61.3% to 100%. Studies in the United States and United Kingdom reported higher susceptibility rates compared to our study (96%–100.0%),[19–22] while studies in Turkey, China, Taiwan, and India reported resistance rates of 20.3, 38.8, 17.5%, and 22.6% respectively.[23–26] In Iranian studies, resistance to TMP/SMX were 10.3% 3.0%,[27,28] which were lower than our study. Indian and Iranian study also revealed molecular mechanism regarding resistance to TMP/SMX.[26,28] A Hungarian study reported a resistant rate to TMP/SMX of 12.1%, similar to our result.[18] In Korea, 2

Table 1

Comparison of *Stenotrophomonas maltophilia* isolated from respiratory and non-respiratory samples.

	Total (no.=1805)	Respiratory samples (no.=1469)	Non-respiratory samples (no.=336)	*P* value
Male	1205 (66.8)	973 (66.2)	232 (69.0)	.336
Age (yr)	65.02 ± 21.01	67.72 ± 19.03	53.24 ± 24.86	< .001
Department				
ICU	682 (37.8)	611 (41.6)	71 (20.8)	< .004
General ward	938 (52.0)	766 (52.1)	172 (51.2)	
ED	145 (8.0)	82 (5.6)	63 (18.8)	
OPD	40 (2.2)	10 (0.7)	30 (8.9)	
Susceptibility (%)	87.7	88.7	84.1	.018

ED = emergency department, ICU = intensive care unit, OPD = out-patient department.

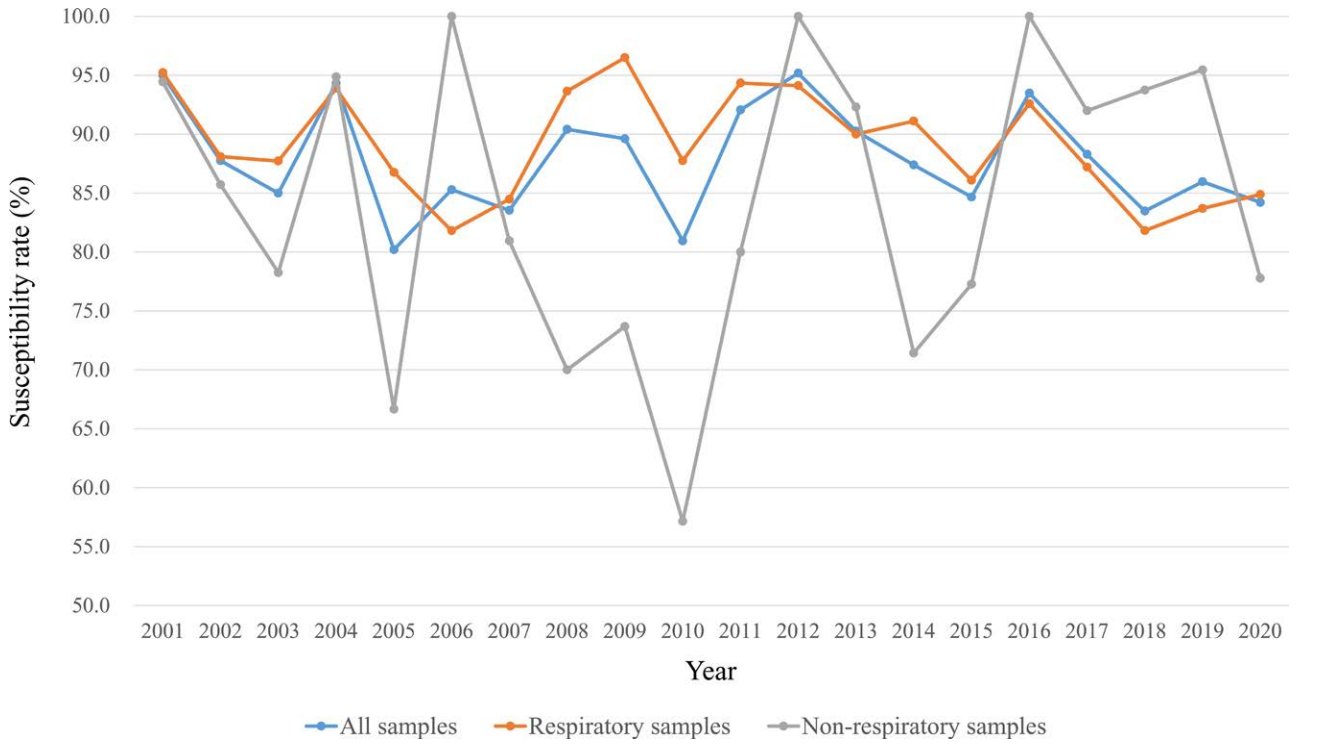

Figure 3. Trimethoprim/sulfamethoxazole susceptibility rates of *Stenotrophomonas maltophilia* over 20 years for all (blue), respiratory (orange), and non-respiratory (gray) samples.

studies examined its susceptibility to TMP/SMX: the former study examined 90 isolates and a latter study examined 206 isolates, and they reported susceptibility rates of 94% and 96%, respectively.[11,12]

There was no significant change in the susceptibility rate over 20 years. A Taiwanese study found no significant change in the susceptibility rate from 1998 to 2008.[25] In the study published in 2016, TMP/SMX resistance were increased from 19.2% in 2005 to 46.9% in 2014.[24] In another study, resistance rate was significantly increased from 29.7% in 2005 to 2009 to 47.1% in 2010 to 2014.[29] Another study analyzing only respiratory samples also found a significant increase in the resistance rate, from 6.3% during 2008 to 2012 and 18.06% during 2013 to 2017.[18] The trend of decreased susceptibility was also shown in our study, from 95.0% in 2001 to 84.2% in 2020. In this study, there was a significant difference between the susceptibility rates of respiratory and non-respiratory samples (88.7% vs 84.1%; $P = .018$). This differs from previous studies that found higher susceptibility in non-respiratory samples. In a 2019 study of respiratory samples, 87.9% of the samples were susceptible to TMP/SMX,[18] while 97.8% and 95.2% of isolates were susceptible to TMP/SMX isolated from the blood samples of bacteremia patients and non-respiratory samples of children, respectively.[19,30] A study conducted at 1 hospital in Brazil reported 68.8% susceptibility for respiratory samples and 81.9% for non-respiratory samples.[31] Another interesting result of our study was that the number of isolates was higher in general ward than that of ICU. That's probably because the absolute number of patients admitted to the ICU was smaller than that to the general ward. The proportion of *S. maltophilia* isolated patients may be higher in ICU.

Because antibiograms vary among regions and countries, knowledge of local antibiograms can promote successful empirical antimicrobial treatment.[32] Susceptibility rates are most accurate when obtained from data accumulated in a clinical microbiology laboratory. The Infectious Diseases Society of America/Society for Healthcare Epidemiology of America antibiotic stewardship program also recommends the use of cumulative antibiograms to establish empirical treatment guidelines.[33] There are several considerations when prescribing TMP/SMX, especially the adverse effects, including hypersensitivity reactions and renal and bone marrow impairment.[34] Although many studies have reported susceptibility rates of over 90%, caution is necessary when interpreting the data and regional susceptibility rates should be checked.

There were some limitations to this study. First, we could not determine whether the isolates were infective or colonizers. Second, we analyzed only susceptibility to TMP/SMX. Guidelines have changed over the 20 years and the list of antibiotics shows annual variations. Therefore, some antibiotics have been tested only for a few of the 20 years. If susceptibility to multiple antibiotics is obtained over a long period, meaningful data can be generated.

In summary, more than 90 *S. maltophilia* isolates were identified per year and a high proportion were isolated from respiratory samples. The rate of susceptibility to TMP/SMX was 87.7% and did not change significantly over 20 years. Isolates from respiratory samples showed significantly higher susceptibility than isolates from non-respiratory samples.

5. Conclusion

Susceptibility analyses using clinical data over long periods can guide the choice of antimicrobial treatment. Because antimicrobial treatment options for *S. maltophilia* infection are limited, clinicians should always consider antimicrobial susceptibility rates.

Authors contributions

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