

Antimicrobial Susceptibility of *Stenotrophomonas maltophilia* Isolates from Korea, and the Activity of Antimicrobial Combinations against the Isolates

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INTRODUCTION

Stenotrophomonas maltophilia is an environmental global emerging Gram-negative multiple-drug-resistant organism that is most commonly associated with respiratory infections (1). Isolation of *S. maltophilia* from human specimens may repre-

The aim of this study was to determine antimicrobial susceptibility of recent clinical *Stenotrophomonas maltophilia* isolates from Korea, and to compare the activity levels of several combinations of antimicrobials. A total of 206 non-duplicate clinical isolates of *S. maltophilia* was collected in 2010 from 11 university hospitals. Antimicrobial susceptibility testing was performed using the Clinical Laboratory Standards Institute agar dilution method. In vitro activity of antimicrobial combinations was tested using the checkerboard method. The susceptibility rates to trimethoprim-sulfamethoxazole and minocycline were 96% and 99%, respectively. The susceptibility rate to levofloxacin was 64%. All of four antimicrobial combinations showed synergy against many *S. maltophilia* isolates. A combination of trimethoprim-sulfamethoxazole plus ticarcillin-clavulanate was most synergistic among the combinations. None of the combinations showed antagonistic activity. Therefore, some of the combinations may be more useful than individual drugs in the treatment of *S. maltophilia* infection. Further clinical studies are warranted to validate our in vitro test results.

Key Words: *Stenotrophomonas maltophilia*; Combination Drug Therapy; Trimethoprim-Sulfamethoxazole; Ticarcillin-Clavulanate

sent colonization rather than infection. Although not highly virulent, *S. maltophilia* can infect immunocompromised hosts and hospitalized patients being predisposed to infection (2). The mortality rates ranged from 14% to 69% in patients with bacteremia by *S. maltophilia* (3, 4). *S. maltophilia* exhibits high-level intrinsic resistance to a broad spectrum of antibiotics, includ-

ing β -lactams, quinolones, aminoglycosides, tetracycline, disinfectants, and heavy metals (5, 6). *S. maltophilia* can also acquire resistance through the uptake of resistance genes located integrons, transposons, and plasmids (7). Therefore, infections caused by *S. maltophilia* are particularly difficult to manage because they show resistance to many classes of antimicrobial agents. The recommended therapeutic agents for *S. maltophilia* infection is trimethoprim-sulfamethoxazole by the evidences of case reports and in vitro susceptibility studies (2). Recently, combinations of antimicrobials have been recommended as treatment for *S. maltophilia* infection, especially in severe septic, neurogenic, debilitated or immunocompromised patients, or when trimethoprim-sulfamethoxazole cannot be used or tolerated (2, 8, 9). However, there is no study focused on the antimicrobial activity of the antibiotics combinations to *S. maltophilia* in Korea.

The aim of this study was to determine antimicrobial susceptibility of recent clinical *S. maltophilia* isolates from Korea, and to compare the activity levels of several combinations of antimicrobials.

MATERIALS AND METHODS

Bacterial strains

A total of 206 non-duplicate clinical isolates of *S. maltophilia* were collected in 2010 from 11 university hospitals. The species were identified using conventional methods and/or the VITEK2 system (bioMerieux, Marcy l’Etoile, France). Among the 206 isolates, 30 were selected for the checkerboard method based on susceptibility: 10 isolates with resistant to trimethoprim-sulfamethoxazole, 26 with resistant to ceftazidime, 22 with nonsusceptible to ticarcillin-clavulanate, and 25 with nonsusceptible to levofloxacin.

Antimicrobial susceptibility test

Antimicrobial susceptibility testing was performed using the CLSI agar dilution method (10). The antimicrobial agents used were trimethoprim-sulfamethoxazole (Dong Wha, Seoul, Korea),

levofloxacin (Daiichi, Tokyo, Japan), moxifloxacin (Bayer Korea, Seoul, Korea), minocycline (SK Chemicals Life Science, Seoul, Korea), tigecycline (Wyeth Research, Pearl River, NY, USA), ceftazidime (Sigma Chemical, St. Louis, MO, USA), ticarcillin-clavulanate (Dong-A, Yongin, Korea), chloramphenicol (Chong Kun Dang, Seoul, Korea), and amikacin (Sigma Chemicals). The breakpoints recommended by CLSI for *S. maltophilia* were applied to interpret the minimum inhibitory concentrations (MICs) (10). *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used as controls.

In vitro activity of antimicrobial combinations

In vitro activity of antimicrobial combinations was tested by the checkerboard method. The antimicrobial combinations tested were trimethoprim-sulfamethoxazole + ticarcillin-clavulanate, levofloxacin + ceftazidime, ceftazidime + amikacin, and ticarcillin-clavulanate + amikacin. Fractional inhibitory concentration (FIC) index was calculated according to the following formula:

$$FIC_A = \frac{\text{MIC of A in combination}}{\text{MIC of A alone}}$$

$$FIC_B = \frac{\text{MIC of B in combination}}{\text{MIC of B alone}}$$

$$FIC \text{ index} = FIC_A + FIC_B$$

The FIC indices were interpreted as follows: ≤ 0.5 , synergistic; > 0.5 to 4, indifferent; > 4 , antagonistic (11).

RESULTS

Antimicrobial susceptibility test

MIC ranges, MIC_{50S}, MIC_{90S}, and the percentages of resistant isolates for various antimicrobial agents are shown in Table 1. The MIC of trimethoprim-sulfamethoxazole ranged from ≤ 0.06 to 128 $\mu\text{g/mL}$, and the MIC₅₀ and MIC₉₀ were 1 and 2 $\mu\text{g/mL}$, respectively. The susceptibility rate was 96%. The MIC of levofloxacin ranged from 0.12 to 64 $\mu\text{g/mL}$, and the MIC₅₀ and MIC₉₀

Table 1. Antimicrobial activity of various antimicrobial agents against *S. maltophilia* by the agar dilution method

Antimicrobial	MIC ($\mu\text{g/mL}$)			Susceptibility (%)		
	Range	50%	90%	S	I	R
Cotrimoxazole	≤ 0.06 -128	1	2	96	-	4
Levofloxacin	0.12-64	2	16	64	16	20
Moxifloxacin	≤ 0.06 -32	0.5	8	-	-	-
Minocycline	0.12-16	0.5	2	99	< 1	< 1
Tigecycline	≤ 0.06 -8	1	4	-	-	-
Ceftazidime	1- > 128	64	> 128	21	8	71
Ticarcillin-clavulanate	1-16	32	> 128	38	38	24
Chloramphenicol	8-128	16	64	7	45	49
Amikacin	≤ 1 - > 128	> 128	> 128	-	-	-

S, susceptible; I, intermediate; R, resistant.

were 2 and 16 µg/mL, respectively, which were higher than those of moxifloxacin (0.5 and 8 µg/mL, respectively). The resistance rate to levofloxacin was 20%. The MIC₅₀ and MIC₉₀ of minocycline were 0.5 and 2 µg/mL, respectively, and only one isolate was resistant to minocycline (the resistance rate < 1%). The MICs of tigecycline ranged from ≤ 0.06 to 8 µg/mL, and the MIC₅₀ and MIC₉₀ were 1 and 4 µg/mL, respectively, which were two-fold higher than those of minocycline. The MIC₅₀ of amikacin was > 128 µg/mL. The MIC₅₀ of ceftazidime 64 µg/mL and the resistance rate was 71%. The MIC₅₀ of ticarcillin-clavulanate was 32 µg/mL and the resistance rate was 24%. The MIC range of chloramphenicol was 8-128 µg/mL, the MIC₅₀ and MIC₉₀ were 16 and 64 µg/mL, respectively. The resistance rate to chloramphenicol was 49%.

In vitro activity of antimicrobial combinations

All of four antimicrobial combinations showed synergy against many *S. maltophilia* isolates. A combination of trimethoprim-sulfamethoxazole plus ticarcillin-clavulanate was most synergistic among the combinations. FIC index of a combination of ticarcillin-clavulanate plus amikacin was 0.38 for 50% of *S. maltophilia* isolates. None of the combinations showed antagonistic activity (Table 2). The FIC index for synergistic *S. maltophilia* ranged 0.09 to 0.5.

Antimicrobial combinations of trimethoprim-sulfamethoxazole plus ticarcillin-clavulanate, ceftazidime plus amikacin, and ticarcillin-clavulanate plus amikacin were synergistic for majority of trimethoprim-sulfamethoxazole-resistant isolates. Trimethoprim-sulfamethoxazole plus ticarcillin-clavulanate demonstrated synergy for the four trimethoprim-sulfamethoxazole-resistant isolates with high MIC levels of trimethoprim-sulfamethoxazole (≥ 64 µg/mL), but MIC values of trimethoprim-sulfamethoxazole did not decrease below susceptibility breakpoints (16-32 µg/mL). On the other hand, synergistic FICs were not found against the two trimethoprim-sulfamethoxazole-resistant isolates with low MIC levels of trimethoprim-sulfamethoxazole (4 µg/mL), but MICs of trimethoprim-sulfamethoxazole in combination with ticarcillin-clavulanate were within susceptible range. Trimethoprim-sulfamethoxazole MICs of trimethoprim-sulfamethoxazole-susceptible isolates for trimethoprim-sulfamethoxazole plus ticarcillin-clavulanate became 2 to 8-fold lower than those used alone (data not shown).

DISCUSSION

Trimethoprim-sulfamethoxazole showed the lowest MIC₉₀ (2 µg/mL) and the isolates showed a high susceptibility rate of 96% to this agent. Trimethoprim-sulfamethoxazole is still considered the treatment of choice for suspected or culture-proven *S. maltophilia* infections. Resistance rates to trimethoprim-sulfamethoxazole have been reported to vary geographically, which were generally less than 10% (2, 12, 13). In this study, all hospitals showed low resistance rate of 5%-10% except one hospital (26%). Some studies with isolates from cystic fibrosis patients and from some Asian countries, such as Taiwan and Turkey, showed high resistance rates (31.3%-100%) (13-25).

In this study, the resistance rate to levofloxacin was 20%, which was higher than the rates of 3% to 11% seen in previous studies (13, 20, 21, 26). Especially, three of hospitals showed high resistance rates over 30%. MIC₉₀ of levofloxacin was also higher than our previous study (27). Moxifloxacin was more active than levofloxacin considering low MICs. Moxifloxacin could be suggested as an alternative to levofloxacin. Further clinical studies are necessary to evaluate the effectiveness of moxifloxacin in treating *S. maltophilia* infections, because there is little data published on the clinical efficacy of moxifloxacin.

The tetracycline derivatives minocycline and tigecycline have shown good in vitro activity against clinical isolates of *S. maltophilia*, but there is little clinical data for treating *S. maltophilia* infections (28, 29). In this study, two isolates were intermediate and one isolate were resistant to minocycline. But, minocycline shows highest in vitro activity against *S. maltophilia* strains, and this data was similar to that of Taiwan, Brazil, Spain, and the USA (16, 21, 22, 30). MICs of tigecycline ranged from ≤ 0.06 to 8 µg/mL, and MIC₅₀ and MIC₉₀ were 1 and 4 µg/mL, respectively. Antimicrobial susceptibilities of a worldwide collection of 1,586 *S. maltophilia* tested against tigecycline, MIC₅₀ and MIC₉₀ of tigecycline were 0.5 and 2 µg/mL (31). The tigecycline in vitro surveillance in Taiwan collected a total of 903 *S. maltophilia*, MIC range of tigecycline was from 0.13 to 16 µg/mL, and MIC₅₀ and MIC₉₀ were 2 and 4 µg/mL (32).

The rates of susceptibility to ceftazidime and ticarcillin-clavulanate were similar with other studies (13-25). The β-lactams and/or β-lactamase inhibitor combinations show little activity against *S. maltophilia*, because the organism has a high intrinsic

Table 2. Activities of antimicrobial combinations against *S. maltophilia*

Antimicrobial combinations	Syn (%)	Ind (%)	Ant (%)	FIC*		
				Range	50%	90%
Cotrimoxazole + ticarcillin-clavulanate	19 (66)	10 (34)	0 (0)	0.16-1.13	0.5	0.75
Levofloxacin + Ceftazidime	10 (34)	19 (66)	0 (0)	0.09-1	0.56	0.75
Ceftazidime + amikacin	15 (52)	14 (48)	0 (0)	0.13-1	0.5	1
Ticarcillin-clavulanate + amikacin	18 (60)	12 (40)	0 (0)	0.16-0.75	0.38	0.75

*50% and 90%, FICs for 50% and 90% of the isolates, respectively. Syn, Synergistic; Ind, indifferent; Ant, antagonistic; FIC, fractional inhibitory concentration.

sic resistance to most penicillins and cephalosporins, and to all carbapenems (7). Chloramphenicol showed similar resistant rate with previous reports, but much lower susceptibility rate due to high intermediate rate (45%) (15, 19, 21, 23).

Considering of the highest MIC, amikacin demonstrated the least active drug to *S. maltophilia* among the tested drugs. The aminoglycosides show poor activity against *S. maltophilia* because of high intrinsic resistance and therefore is not useful in monotherapy (7).

Because of historical evidence, case reports and high in vitro susceptibility rates, cotrimoxazole is usually considered the treatment of choice for *S. maltophilia* infection (2). However, increasing resistance to cotrimoxazole and the alternate antimicrobials may cause problems for the empirical treatment of *S. maltophilia* infections. Therefore, combination therapy may be indicated in the setting of severe sepsis, neutropenia or polymicrobial infections, but clinical evidence is still lacking (2, 7). Combination therapy may be more practical when cotrimoxazole therapy is contraindicated. We assessed the activity of four antimicrobial combinations by the checkerboard method, since these combinations had been reported to have synergistic effects to *S. maltophilia* (7). Synergistic effect was demonstrated by all combinations (34%-66%) (Table 2). Synergy for trimethoprim-sulfamethoxazole resistant *S. maltophilia* isolates were shown by trimethoprim-sulfamethoxazole plus ticarcillin-clavulanate (4/6), ceftazidime plus amikacin (4/6), and ticarcillin-clavulanate plus amikacin (5/6).

Poulos et al. (33) demonstrated synergy between trimethoprim-sulfamethoxazole and ticarcillin-clavulanic acid by the checkerboard method and by the time-kill assay in 19 different trimethoprim-sulfamethoxazole-resistant strains. In our study, synergistic activities by trimethoprim-sulfamethoxazole plus ticarcillin-clavulanate were shown in 67% of trimethoprim-sulfamethoxazole-resistant *S. maltophilia*, MIC values of trimethoprim-sulfamethoxazole were not decreased below susceptible breakpoint. Likewise, other antimicrobial combinations (ceftazidime plus amikacin, ticarcillin-clavulanate plus amikacin) were synergistic, MIC value of each antibiotic agent sometimes was not clearly decreased (data not shown). Antibiotics for combination therapy should be chosen on the basis of in vitro susceptibility test (7). Therefore, it is uncertain and needs to be evaluated that combination therapy with trimethoprim-sulfamethoxazole plus ticarcillin-clavulanate inhibit the growth in vivo of trimethoprim-sulfamethoxazole resistant *S. maltophilia*.

Although the choice of monotherapy or combination therapy is a controversial issue, several authors suggest combination treatment, especially in patients at risk (2, 7). Synergy testing may help determine the most appropriate combination in each special setting, but the problem is a lack of standardization of the techniques to determine synergy (34). Clinical data of in vivo combination therapy should be warranted.

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