

# Clinical Factors Associated with Acquisition of Resistance to Levofloxacin in *Stenotrophomonas maltophilia*

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**Purpose:** Fluoroquinolones, rapidly gaining prominence in treatment of *Stenotrophomonas maltophilia* (SMP), are noted for their potency and tolerability. However, SMP may rapidly acquire resistance to fluoroquinolones. We evaluated associations of clinical factors with acquisition of levofloxacin resistance (LF<sup>r</sup>) in SMP. **Materials and Methods:** Our retrospective cohort study was based on patient data collected between January 2008 and June 2010. Through screening of 1275 patients, we identified 122 patients with data for SMP antibiotic susceptibility testing in  $\geq 3$  serial SMP isolates. **Results:** We assigned the 122 patients to either the SS group (n=54) in which levofloxacin susceptibility was maintained or the SR group (n=31) in which susceptible SMP acquired resistance. In multivariate regression analysis, exposure to levofloxacin for more than 3 weeks [odds ratio (OR) 15.39, 95% confidential interval (CI) 3.08–76.93,  $p=0.001$ ] and co-infection or co-colonization with *Klebsiella pneumoniae* resistant to levofloxacin (OR 4.85, 95% CI 1.16–20.24,  $p=0.030$ ) were independently associated with LF<sup>r</sup> acquisition in SMP. **Conclusion:** Acquisition of LF<sup>r</sup> during serial sampling of SMP was related to the levofloxacin exposure.

**Key Words:** *Stenotrophomonas maltophilia*, fluoroquinolones, levofloxacin, drug resistance

## INTRODUCTION

*Stenotrophomonas maltophilia* (*S. maltophilia*) is an emergent pathogen in health-care facilities worldwide, causing mainly pneumonia or septicemia related or unrelated to catheter use. Patients with immunodeficiency are especially at risk.<sup>1-3</sup> Serious infection attributed to *S. maltophilia* is a significant cause of mortality in patients with hematologic malignancies,<sup>4</sup> with mortality rates up to 37.5%.<sup>5</sup>

*S. maltophilia* is intrinsically resistant to antibiotics that could be excluded by multidrug efflux pumps and/or inactivated by  $\beta$ -lactamase and aminoglycoside-modifying enzymes.<sup>6</sup> Trimethoprim-sulfamethoxazole (TMP-SMX), historically the first line of defense in *S. maltophilia* infection,<sup>7</sup> may induce resistance related to class 1 integrons containing the *sulI* sulfonamide resistance gene and insertion

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element common region elements containing the *sul2* resistance gene.<sup>6,8,9</sup> However, rates reported for resistance to TMP-SMX in *S. maltophilia* are generally less than 10%.<sup>10-12</sup>

Clinically, the use of TMP-SMX in *S. maltophilia* infection is limited by adverse effects of the drug, including skin eruptions, hepato- and renal toxicity, and bone marrow suppression.<sup>7,13</sup> Additionally, resistance to TMP-SMX in *S. maltophilia* is increasing at certain centers.<sup>8,13</sup>

Fluoroquinolones, including levofloxacin and moxifloxacin, are an attractive alternative for treating *S. maltophilia* infection, because they are well-tolerated and effective, compared to TMP-SMX, and because of their low rates of microbial resistance.<sup>7,11,13-16</sup> However, *S. maltophilia* can rapidly acquire resistance to fluoroquinolones, especially in monotherapy, and this may limit their use in combination therapy.<sup>17</sup> In this study, we investigated the poorly understood relationships between clinical factors and the acquisition of levofloxacin resistance in *S. maltophilia*.

## MATERIALS AND METHODS

### Subjects and study design

This retrospective cohort study was conducted at Severance Hospital, a 2000-bed university-affiliated teaching hospital and tertiary care referral center in Seoul, South Korea, based on data collected from January 2008 to June 2010. Patients who met all of the following conditions were eligible for this study: 1) age 18 years old or older; 2) ≥3 serial isolations of *S. maltophilia* by culture, accompanied by *in vitro* antimicrobial susceptibility testing (AST) in any clinical specimen; and 3) results for three or more consecutive ASTs of *S. maltophilia* for levofloxacin in clinical specimens from the same system (e.g., the respiratory, urinary or biliary tract, peritoneal or pleural fluid, or an external wound) at intervals from 3 days to 3 months.

We screened the data for 3029 *S. maltophilia* isolates from 1275 patients, and identified 528 isolates with data for serial isolation and all AST results from 122 patients (Fig. 1). We stratified these 122 patients into either the SS group (n=54) whose records showed maintenance of levofloxacin susceptibility from the first *S. maltophilia* isolate to the last isolate recorded or the SR group (n=31) with data confirming transition from levofloxacin susceptibility to resistance in serial *S. maltophilia* isolates. However, we excluded an RR group (85 isolates from 21 patients) whose records revealed the maintenance of levofloxacin resistance from the first *S. maltophilia* isolate to the last isolate recorded from our study analysis. Additionally, patients (12 isolates from 4 patients) with data confirming transition from levofloxacin resistance to susceptibility and patients (86 isolates from 12 patients) with inconstant AST results for levofloxacin were excluded from the analysis (Fig. 1).

### *In vitro* antimicrobial susceptibility testing

All bacterial species were identified using conventional methods and/or the ATB 32GN system (bioMérieux, Marcy l’Etoile, France). Antimicrobial susceptibility was tested by the Clinical and Laboratory Standards Institute (CLSI) agar dilution method.<sup>18</sup> The antimicrobial agents used for AST were TMP-SMX (Dong Wha Pharmaceutical Co. Ltd., Seoul, Korea); levofloxacin (Daiichi Sankyo Co. Ltd., Tokyo, Japan); minocycline (SK Chemicals Co. Ltd., Life Sciences, Seoul, Korea); ceftazidime, amikacin, and gentamicin (Sigma Chemical Co., St. Louis, MO, USA); tigecycline (Wyeth Research, Pearl River, NY, USA); imipenem (Choongwae Pharma Corp., Seoul, Korea); and piperacillin/tazobactam (Yuhan Co. Ltd., Seoul, Korea).

### Definitions

The index isolate was defined as the last levofloxacin-susceptible isolate cultured from a patient in the SS group and

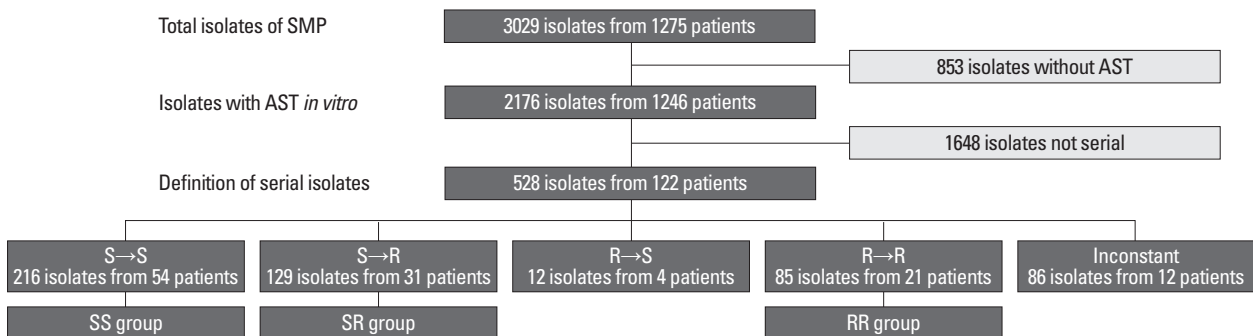


Fig. 1. Selection of *S. maltophilia* isolates and patients. SMP, *Stenotrophomonas maltophilia*; AST, antimicrobial susceptibility test; S, susceptible; R, resistant.

as the first levofloxacin-resistant isolate from one patient in the SR group.

### Data collection

The clinical data at the time of identification of the index isolate were collected through review of electronic medical records. Coexisting conditions of interest included length of hospital stay, intensive care unit admission, use of mechanical ventilation, current tracheostomy status, acute renal failure (ARF) with renal replacement therapy (RRT), neutropenia, and steroid or immunosuppressant use, as well as the Charlson's comorbidity index score. We recorded the history and total duration of all systemic antibiotic exposures within 3 months from identification of the index isolate. To evaluate the effect of co-infection or co-colonization with other bacteria on the acquisition of resistance to levofloxacin in *S. maltophilia*, the data for co-infection or co-colonization were evaluated in parallel with results of AST for fluoroquinolones.

### Statistical analysis

Categorical data are expressed as a number (percent). If the

continuous variables had normal distribution, these were expressed as mean±standard deviation. Continuous variables without normal distribution were expressed as median (interquartile range). We used Student's t-test or Mann-Whitney U test and the  $\chi^2$  test or Fisher's exact test to compare continuous and categorical variables, respectively, in a univariate analysis of clinical characteristics in the SR and SS groups. Variables with *p*-values less than 0.10 in univariate analysis were included in a multivariate logistic regression analysis to identify clinical factors associated with acquisition of levofloxacin resistance in *S. maltophilia*. Results from the multivariate analysis are expressed as an odds ratio (OR) and 95% confidence intervals (CIs). A two-tailed *p*-value <0.05 was taken to indicate significance. All statistical analyses were performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

## RESULTS

The SS and SR groups were similar in age and gender (Table 1). A significantly higher proportion of patients in the SR group than in the SS group were in ARF requiring RRT

**Table 1.** Clinical Characteristics of the Study Population and Subgroups SS, Defined as the Maintenance of Levofloxacin Susceptibility, and SR, Defined as a Change from Levofloxacin Susceptibility to Resistance

Characteristics	Total (n=85)	SS group (n=54)	SR group (n=31)	<i>p</i> value
Age, yrs	62.7±14.4	61.5±14.4	64.8±14.4	0.314*
Gender, male	61 (71.8)	37 (68.5)	24 (77.4)	0.380 <sup>†</sup>
Clinical specimen, yes				
Respiratory tract	56 (65.9)	35 (64.8)	21 (67.7)	
Biliary tract	10 (11.8)	7 (13.0)	3 (9.7)	
External wound	8 (9.4)	6 (11.1)	2 (6.5)	
Intraperitoneal space	7 (8.2)	4 (7.4)	3 (9.7)	
Urinary tract	3 (3.5)	1 (1.9)	2 (6.5)	
Pleural space	1 (1.2)	1 (1.9)	0 (0.0)	
Hospital stay, days	65.0 (37.5–93.5)	62.5 (35.5–81.2)	76.0 (38.0–121.0)	0.267 <sup>‡</sup>
ICU admission, yes	60 (70.6)	36 (66.7)	24 (77.4)	0.295 <sup>†</sup>
Mechanical ventilation, yes	53 (62.4)	31 (57.4)	22 (71.0)	0.214 <sup>†</sup>
Tracheostomy, yes	46 (54.1)	30 (55.6)	16 (51.6)	0.725 <sup>†</sup>
ARF on RRT, yes	12 (14.1)	4 (7.4)	8 (25.8)	0.026 <sup>§</sup>
Neutropenia, yes	4 (4.7)	2 (3.7)	2 (6.5)	0.620 <sup>§</sup>
Corticosteroid use, yes	31 (36.5)	17 (31.5)	14 (45.2)	0.207 <sup>†</sup>
Immunosuppressant use, yes	4 (4.7)	2 (3.7)	2 (6.5)	0.620 <sup>§</sup>
Charlson's comorbidity index	3 (2–5)	3 (2–6)	3 (2–5)	0.417 <sup>‡</sup>

ICU, intensive care unit; ARF, acute renal failure; RRT, renal replacement therapy.

Data are expressed as the mean±SD or number (percent) or median (interquartile range).

\*Student's t-test.

<sup>†</sup> $\chi^2$ -test.

<sup>‡</sup>Mann-Whitney U test.

<sup>§</sup>Fisher's exact test.

(25.8% vs. 7.4%,  $p=0.026$ ). Other coexisting conditions did not differ significantly between the two groups (Table 1).

The total duration of exposure to levofloxacin within 3 months from identification of the index isolate was significantly longer in the SR group [33 (9–42) days] than the SS group [11 (4–64) days,  $p=0.044$ ] (Table 2). However, the total duration of exposure to anti-pseudomonal penicillins, 3rd cephalosporins, 4th cephalosporins, ciprofloxacin, carbapenems, aminoglycosides, glycopeptides, and metronidazole did not show significant differences between the SS and SR groups (Table 2). Co-infection or co-colonization with ciprofloxacin-resistant *Staphylococcus aureus* was significantly more common in the SS group than in the SR group (31.5% vs. 9.7%,  $p=0.032$ ). The SR group had significantly higher percentages of co-infection or co-colonization with any gram-negative bacteria and with *Klebsiella pneumoniae* resistant to levofloxacin (58.1% vs. 35.2%,  $p=0.041$ ; 32.3% vs. 9.3%,  $p=0.007$ , respectively) (Table 3).

In the final multivariate logistic regression analysis, exposure to levofloxacin for more than 3 weeks (OR 15.39, 95% CI 3.08–76.93,  $p=0.001$ ) and co-infection or co-colonization with *K. pneumoniae* resistant to levofloxacin (OR 4.85, 95% CI 1.16–20.24,  $p=0.030$ ) were clinical factors independently associated with the acquisition of resistance to levofloxacin in *S. maltophilia* (Table 4).

## DISCUSSION

This study confirmed the acquisition of levofloxacin resistance in *S. maltophilia* during clinical application of the drug. *S. maltophilia* may potentially develop resistance to

fluoroquinolones through various mechanisms, including 1) efflux pump systems, such as SmeABC and SmeDEF,<sup>19,20</sup> or 2) mutations in outer-membrane porin proteins.<sup>21</sup> A previous study suggested that spontaneous mutations conferring resistance to fluoroquinolones occur at frequencies between  $10^{-5}$  to  $10^{-752}$  after quinolones therapy in *S. maltophilia*.<sup>22</sup> In a clinical study at the MD. Anderson Cancer Center, use of fluoroquinolones in the previous 90 days was independently associated with emergence of multidrug resistant *S. maltophilia* infection in cancer patients.<sup>23</sup> In a case-control study, Spanik, et al.<sup>24</sup> found a positive association of prophylactic fluoroquinolones use with bacteremia by MDR gram-negative bacilli including *S. maltophilia* in neutropenic cancer patients. Thus experimental and clinical data from multiple studies, including this one, associate fluoroquinolones exposure with acquired resistance to fluoroquinolones in *S. maltophilia*.

Co-infection or co-colonization with levofloxacin-resistant *K. pneumoniae* presented another independent clinical factor in acquisition of levofloxacin resistance in *S. maltophilia*. Co-infection and co-colonization with other bacterial species, especially those with resistance to fluoroquinolones, are clinically relevant because the species may actively exchange drug resistance genes by means of plasmids and transposons.<sup>25</sup> Clinical co-infection of *S. maltophilia* with other pathogens (e.g., other glucose-non-fermenting gram-negative bacteria including *Pseudomonas aeruginosa*, *Burkholderia* species and *Acinetobacter baumannii*; *Enterobacteriaceae* including *Escherichia coli*, *Klebsiella* species and *Enterobacter* species; *Staphylococcus aureus* including methicillin-resistant *S. aureus*; *Enterococcus* species; *Bacteroides* species; and *Candida albicans*) is confirmed through

**Table 2.** Total Duration of Systemic Antibiotic Exposure within 3 Months from Identification of the Index Isolate in Patient Groups SS Was Defined as the Maintenance of Levofloxacin Susceptibility and SR Was Defined as a Change from Levofloxacin Susceptibility to Resistance

Antibiotics, total exposed duration, days	Total (n=85)	SS group (n=54)	SR group (n=31)	<i>p</i> value*
Anti-pseudomonal penicillins	22 (10–33)	24 (7–35)	21 (11–31)	0.911
3rd cephalosporins	28 (12–63)	44 (19–71)	28 (11–49)	0.110
4th cephalosporins	18 (9–35)	18 (3–45)	18 (10–29)	1.000
Ciprofloxacin	20 (11–31)	19 (8–33)	20 (14–30)	0.564
Levofloxacin	24 (7–46)	11 (4–64)	33 (9–42)	0.044
Carbapenems	12 (3–31)	17 (1–43)	12 (3–30)	0.736
Aminoglycosides	26 (13–49)	26 (14–80)	25 (12–43)	0.193
Glycopeptides	14 (6–36)	23 (8–46)	12 (5–31)	0.149
Metronidazole	25 (11–49)	21 (7–38)	30 (3–48)	0.440

Data are expressed as the median (interquartile range).

\*Mann-Whitney U test.

**Table 3.** Characteristics of Co-Infecting and Co-Colonizing Microorganisms in Patient Subgroups SS, Defined as the Maintenance of Levofloxacin Susceptibility, and SR, Defined as a Change from Levofloxacin Susceptibility to Resistance

Microorganisms and their sensitivity to selected antibiotics	Total (n=85)	SS group (n=54)	SR group (n=31)	p value
Any Gram-positive	46 (54.1)	31 (57.4)	15 (48.4)	0.422*
Ciprofloxacin (R)	35 (41.2)	25 (46.3)	10 (32.3)	0.206*
<i>Staphylococcus aureus</i>	24 (28.2)	19 (35.2)	5 (16.1)	0.060 <sup>†</sup>
Ciprofloxacin (R)	20 (23.5)	17 (31.5)	3 (9.7)	0.032 <sup>†</sup>
Coagulase-negative staphylococci	18 (21.2)	13 (24.1)	5 (16.1)	0.388 <sup>†</sup>
Ciprofloxacin (R)	7 (8.2)	6 (11.1)	1 (3.2)	0.414 <sup>†</sup>
<i>Enterococcus sp.</i>	21 (24.7)	12 (22.2)	9 (29.0)	0.483*
Ciprofloxacin (R)	17 (20.0)	9 (16.7)	8 (25.8)	0.311*
Norfloxacin (R)	7 (8.2)	4 (7.4)	3 (9.7)	0.702 <sup>†</sup>
Any FQ (R)	18 (21.2)	10 (18.5)	8 (25.8)	0.429*
Any gram-negative	64 (75.3)	41 (75.9)	23 (74.2)	0.859*
Ciprofloxacin (R)	29 (34.1)	18 (33.3)	11 (35.5)	0.840*
Levofloxacin (R)	37 (43.5)	19 (35.2)	18 (58.1)	0.041*
Any FQ (R)	44 (51.8)	25 (46.3)	19 (61.3)	0.183*
<i>Acinetobacter baumannii</i>	28 (32.9)	20 (37.0)	8 (25.8)	0.289*
Ciprofloxacin (R)	7 (8.2)	5 (9.3)	2 (6.5)	1.000 <sup>†</sup>
Levofloxacin (R)	16 (18.8)	9 (16.7)	7 (22.6)	0.502*
Any FQ (R)	20 (23.5)	13 (24.1)	7 (22.6)	0.876*
<i>Pseudomonas aeruginosa</i>	36 (42.4)	23 (42.6)	13 (41.9)	0.953*
Ciprofloxacin (R)	24 (28.2)	13 (24.1)	11 (35.5)	0.261*
Levofloxacin (R)	7 (8.2)	2 (3.7)	5 (16.1)	0.094 <sup>†</sup>
Any FQ (R)	24 (28.2)	13 (24.1)	11 (35.5)	0.261*
<i>Klebsiella pneumoniae</i>	21 (24.7)	9 (16.7)	12 (38.7)	0.023*
Levofloxacin (R)	15 (17.6)	5 (9.3)	10 (32.3)	0.007 <sup>†</sup>
<i>Escherichia coli</i>	9 (10.6)	7 (13.0)	2 (6.5)	0.476 <sup>†</sup>
Levofloxacin (R)	5 (5.9)	4 (7.4)	1 (3.2)	0.648 <sup>†</sup>
<i>Enterobacter spp.</i>	16 (18.8)	12 (22.2)	4 (12.9)	0.392 <sup>†</sup>
Levofloxacin (R)	6 (7.1)	4 (7.4)	2 (6.5)	1.000 <sup>†</sup>
<i>Serratia marcescens</i>	10 (11.8)	6 (11.1)	4 (12.9)	1.000 <sup>†</sup>
Levofloxacin (R)	4 (4.7)	2 (3.7)	2 (6.5)	0.620 <sup>†</sup>
Other gram-negatives	21 (24.7)	14 (25.9)	7 (22.6)	0.731*
Ciprofloxacin (R)	1 (1.2)	0 (0.0)	1 (3.2)	0.365 <sup>†</sup>
Levofloxacin (R)	4 (4.7)	1 (1.9)	3 (9.7)	0.135 <sup>†</sup>
Any FQ (R)	4 (4.7)	1 (1.9)	3 (9.7)	0.135 <sup>†</sup>

FQ, fluoroquinolones; R, resistant.

Data are expressed as the number (percent).

\* $\chi^2$ -test.<sup>†</sup>Fisher's exact test.**Table 4.** Multivariate Logistic Regression Analysis of Factors Related to Acquisition of Levofloxacin Resistance in *S. maltophilia*

Variables	OR	95% CI	p value
ARF on RRT	3.95	0.66-23.65	0.132
Co-infection/co-colonization			
<i>S. aureus</i> , ciprofloxacin (R)	0.26	0.06-1.24	0.091
<i>K. pneumoniae</i> , levofloxacin (R)	4.85	1.16-20.24	0.030
<i>P. aeruginosa</i> , levofloxacin (R)	1.36	0.37-2.49	0.475
Total exposed duration to levofloxacin, $\geq 3$ wks	15.39	3.08-76.93	0.001

OR, odds ratio; CI, confidential interval; ARF, acute renal failure; RRT, renal replacement therapy; R, resistant.

recovery of multiple species from patient samples.<sup>26-29</sup> *S. maltophilia* can also exchange antibiotic-resistance genes with gram-positive and other gram-negative bacteria.<sup>30</sup> The *Smqnr* gene present in the bacterial chromosome contributes to intrinsic quinolones resistance in *S. maltophilia*.<sup>31</sup> Although *S. maltophilia* isolates harboring *Smqnr* genes could serve as a reservoir for horizontal transfer of these genes into *Enterobacteriaceae*, this event is unlikely to occur because plasmids containing *Smqnr* are unstable.<sup>21,32</sup> As the possibility and mechanism for the transfer of levofloxacin resistance gene from other gram-negative bacteria to *S. maltophilia* have not been fully evaluated, further *in vitro* study is warranted to verify the association of *S. maltophilia* with *K. pneumoniae* with levofloxacin resistance.

To our knowledge, no study has systematically evaluated clinical factors that influence acquisition of levofloxacin resistance in *S. maltophilia*. To identify such factors, we followed levofloxacin susceptibility in serial isolates of *S. maltophilia* from 122 individual patients (i.e., longitudinally) and compared characteristics of patient subgroups in which susceptibility was maintained (the SS group) and not maintained (the SR group). Although patients with cystic fibrosis usually suffer the respiratory tract infection with *S. maltophilia*, there were not any patients with cystic fibrosis in this study because of the extremely low prevalence of cystic fibrosis in South Korea.<sup>33</sup>

The limitations of our study include the retrospective design with data from a single center only and the non-standardization of protocols for antimicrobial sensitivity testing in *S. maltophilia*. The results of an AST performed by disc diffusion, an E-test, and agar dilution may vary and may not correlate with *in vivo* effectiveness.<sup>34</sup> The British Society for Antimicrobial Chemotherapy (BSAC) recommends only disk diffusion and agar dilution testing for TMP-SMX, while the CLSI generally recommends only disk diffusion testing and agar dilution testing for TMP-SMX, levofloxacin, and minocycline.<sup>18</sup> We performed AST using the most recent revision of CLSI recommendations, the guideline that is most widely available. We further assumed that transitions between CLSI and BSAC recommendations for the AST would not affect the results of our regression analysis.

In conclusion, appropriate restrictions on the use of levofloxacin, currently among the commonly used antibiotics for *S. maltophilia* infection, may be necessary to prevent the emergence of levofloxacin resistance in *S. maltophilia*. Further study of this resistance through molecular epidemiologic analysis may clarify these clinical findings.

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