

Monotherapy with Fluoroquinolone or Trimethoprim-Sulfamethoxazole for Treatment of *Stenotrophomonas maltophilia* Infections

Yu Lin Wang, Marco R. Scipione, Yanina Dubrovskaya, John Papadopoulos

Department of Pharmacy, NYU Langone Medical Center, New York, New York, USA

The treatment of choice for *Stenotrophomonas maltophilia* is trimethoprim-sulfamethoxazole (SXT). Fluoroquinolones (FQs) have *in vitro* activity against *S. maltophilia*; however, there is limited published information on their effectiveness. The purpose of this study is to compare the effectiveness of FQs and SXT for the treatment of *S. maltophilia*. A retrospective review of 98 patients with *S. maltophilia* infections who received SXT or FQ monotherapy was conducted. Patients ≥ 18 years old with a positive culture for *S. maltophilia* and clinical signs of infection who received treatment for ≥ 48 h were included. Microbiological cure and clinical response were evaluated at the end of therapy (EOT). In-hospital mortality and isolation of nonsusceptible isolates were also evaluated. Thirty-five patients received SXT, and 63 patients received FQ; 48 patients received levofloxacin, and 15 patients received ciprofloxacin. The most common infection was pulmonary. The overall microbiological cure rate at EOT was 63%. Thirteen of 20 patients (65%) who received SXT and 23 of 37 patients (62%) who received FQ had microbiological cure at EOT ($P = 0.832$). The overall clinical success rate was 55%, 52% for those who received FQ and 61% for those who received SXT ($P = 0.451$). In-hospital mortality was 24%, with similar rates in the two groups (25% for FQ versus 22% for SXT; $P = 0.546$). Development of resistance on repeat culture was 30% for FQ and 20% for SXT ($P = 0.426$). Fluoroquinolone and SXT monotherapies may be equally effective for the treatment of *S. maltophilia* infections. Resistance was documented in subsequent isolates of *S. maltophilia* in both groups.

Stenotrophomonas maltophilia is an aerobic, nonfermentative, Gram-negative bacillus formerly called *Xanthomonas maltophilia* or *Pseudomonas maltophilia*. It is an environmental organism found in water and soil and on plants and has emerged as an important nosocomially acquired pathogen (1). It is generally considered to be an opportunistic pathogen and is known to cause pneumonia, bacteremia, catheter-related infections, and intra-abdominal infections (2). Patients at risk for developing infections with *S. maltophilia* include transplant patients on immunosuppressants, cancer patients receiving chemotherapy, neutropenic patients, and patients with AIDS (3). Additional risk factors for *S. maltophilia* infections include extended use of indwelling catheters, such as endotracheal tubes and genitourinary catheters; recent broad-spectrum antibiotic therapy, including carbapenems; and prolonged hospital stay (3). Although *S. maltophilia* is sometimes thought to be a colonizer, it can cause infections in susceptible patients with multiple risk factors. Due to the increase in the patient population at risk, the incidence of *S. maltophilia* infections may be increasing (1, 4). Mortality rates associated with *S. maltophilia* bacteremia range from 14 to 62%, with an attributable mortality of 20 to 30% (4–13). Treatment of *S. maltophilia* infections can be difficult, as *S. maltophilia* is inherently resistant to many classes of antibiotics, including β -lactams and aminoglycosides. Antibiotics with *in vitro* activity against *S. maltophilia* include trimethoprim-sulfamethoxazole (SXT), fluoroquinolones (FQs), tetracyclines, ticarcillin-clavulanate, and ceftazidime; however, there are limited clinical data on the use of these agents (6–10, 14). Trimethoprim-sulfamethoxazole continues to be a primary choice for the treatment of *S. maltophilia*, but FQs are an attractive option due to *in vitro* activity (15). The purpose of this study was to evaluate patients with *S. maltophilia* infections and assess the effectiveness of treatment with FQ monotherapy compared to SXT monotherapy.

MATERIALS AND METHODS

Study design. This was a retrospective study of patients with *S. maltophilia* infections who received monotherapy with SXT or an FQ. The study population included patients with positive cultures for *S. maltophilia* who were 18 years of age or older with clinical signs and symptoms of infection according to CDC definitions of nosocomial infections (16). The patients must have received treatment directed at *S. maltophilia* for at least 48 h. Patients were excluded if they received combination therapy for *S. maltophilia*. All patients with positive cultures for *S. maltophilia* were identified from microbiological reports from January 2008 to December 2011. Antimicrobial susceptibility and MICs were determined via Vitek-2 (bioMérieux), Etest, or disk diffusion.

Data. Demographic information was collected from the patients' electronic medical records, including underlying illnesses, presence of indwelling devices, immunosuppression, and prior antibiotic use. Microbiological cure at the end of therapy (EOT), clinical response at EOT, in-hospital and 30-day mortality, and isolation of a nonsusceptible isolate within 30 days of EOT were evaluated. The clinical response at EOT was evaluated by two investigators (Y.L.W. and M.R.S.) and determined by improvement in all signs and symptoms of infection with no further treatment required. Patients were not included in the analysis for this endpoint if we could not determine a definite response. Microbiological cure was defined as a negative culture, from the same site as the original positive culture, at or prior to the EOT. Patients who did not have a repeat culture were excluded from analysis for this endpoint.

Received 21 June 2013 Returned for modification 4 September 2013

Accepted 12 October 2013

Published ahead of print 21 October 2013

Address correspondence to Marco R. Scipione, marco.scipione@nyumc.org, or Yu Lin Wang, yulin.wang@nyumc.org.

Copyright © 2014, American Society for Microbiology. All Rights Reserved.

doi:10.1128/AAC.01324-13

Statistical analysis. Categorical variables were analyzed using a chi-square or Fisher exact test. Continuous variables were analyzed using Student's *t* test or the Mann-Whitney U test. A *P* value of <0.05 denoted statistical significance. Multivariate logistic regression was done in a backward stepwise manner to determine if there was a significant association with in-hospital mortality for any variable with a significant association in univariate analysis. Data were analyzed using SPSS software version 20.0 (IBM Corp., Somers, NY).

RESULTS

A total of 98 patients were evaluated, with a mean age of 73 ± 15 years. Thirty-five patients received SXT, and 63 patients received an FQ; 48 patients received levofloxacin, and 15 received ciprofloxacin. Forty-two (43%) patients had recent major surgery and were admitted to the surgical service at the time of the *S. maltophilia* culture. Twenty-three (24%) patients were in the intensive care unit (ICU) at the time of culture. The most common underlying comorbid conditions for all patients were solid organ malignancy (39%), coronary artery disease (38%), diabetes mellitus (36%), chronic kidney disease (26%), and pulmonary disease (26%). Only a small number of patients were immunocompromised, with chemotherapy being the most common cause of immunosuppression. The most common type of indwelling device was a genitourinary catheter (34%), followed by an endotracheal tube (30%) and central venous catheter (CVC) (14%). Most baseline demographic characteristics were similar for patients who received SXT or FQ, although more patients who received SXT had an intra-abdominal drain (17% versus 2%; *P* = 0.004) (Table 1). The baseline characteristics for patients who received levofloxacin or ciprofloxacin were similar, except that more patients who received levofloxacin had prior antibiotic use, including cephalosporin use, and they were more likely to be in the ICU at the time of culture. Pulmonary infections accounted for 56% of all *S. maltophilia* infections. There were 17 (49%) pulmonary infections in patients who received SXT and 38 (60%) in patients who received an FQ. Overall, 19 (19%) patients had a skin/skin structure infection (SSSI), 9 (9%) patients had a urinary tract infection, 9 (9%) patients had an intra-abdominal infection, and 6 (6%) patients had bacteremia, 3 cases of which were related to a CVC.

Eighty-two (84%) patients received an antibiotic prior to isolation of *S. maltophilia*. Cephalosporins (49%), penicillins (48%), and carbapenems (30%) were the most commonly used antibiotics prior to culture. Patients who were treated with an FQ were more likely to have received a cephalosporin in the previous 30 days for prior conditions (57% versus 34%; *P* = 0.030), and patients who were treated with SXT were more likely to have received levofloxacin than other FQs in the previous 30 days for prior conditions (63% versus 22%; *P* = 0.041). Seventy-five (77%) patients had a polymicrobial infection. More patients who were treated with an FQ had a polymicrobial infection (84% versus 63%; *P* = 0.017), including polymicrobial infection with a Gram-negative organism (46% versus 26%; *P* = 0.048). *Pseudomonas aeruginosa* was the most common Gram-negative organism that was isolated in both groups. Based on *in vitro* susceptibility testing, SXT and minocycline had the highest susceptibility rates among all *S. maltophilia* isolates tested, with 96% susceptible to SXT and 95% susceptible to minocycline. Levofloxacin showed modest susceptibility (82%), while ceftazidime and ticarcillin-clavulanate had poor susceptibilities (49% and 40%, respectively) (Table 2). The length of stay prior to culture for all patients was 5 days (interquartile range [IQR], 1 to 15 days), and the values were similar for

patients who received an FQ or SXT (6 days [IQR, 1 to 19 days] versus 4 days [IQR, 0 to 11 days]; *P* = 0.786). The number of days prior to initiation of targeted *S. maltophilia* treatment was 3 days (IQR, 2 to 4 days) in all patients. The median length of stay was 25 days (IQR, 15 to 37 days) for patients who received an FQ compared to 16 days (IQR, 8 to 42 days) for those who received SXT (*P* = 0.970). The median duration of therapy was 9 days (IQR, 2 to 38 days) for patients who received an FQ and 8 days (IQR, 2 to 28 days) for patients who received SXT (*P* = 0.265). The median daily dose was 7.8 mg/kg of body weight/day of the trimethoprim (TMP) component for SXT, 500 mg/day for levofloxacin, and 1,000 mg/day for oral ciprofloxacin.

Microbiological cure in patients who had a repeat culture was achieved at EOT in 63% (36/57) of all patients, 62% (23/37) of patients who received an FQ, and 65% (13/20) of patients who received SXT (*P* = 0.832) (Table 3). Ten of 14 (71%) isolates tested that were recovered at EOT were resistant to levofloxacin, and 0 of 11 (0%) that were tested were resistant to SXT following FQ monotherapy (*P* = 0.11). Two of 5 (40%) isolates tested that were recovered at EOT were resistant to levofloxacin, and 2 of 7 (28%) that were tested were resistant to SXT following SXT monotherapy (*P* = 0.14). Clinical success at EOT was 55% overall, and the rates were similar in the two treatment groups. Patients who receive an FQ had a 30-day mortality rate of 31% compared to 22% for patients who received SXT (*P* = 0.42). In-hospital mortality was 25% for patients who received an FQ compared to 20% for patients who received SXT (*P* = 0.55). Eleven of 37 patients (30%) who had a repeat culture after receiving an FQ had a nonsusceptible isolate identified within 30 days of EOT compared to 4 of 20 patients (20%) who received SXT (*P* = 0.426). For patients who had a repeat culture, the number of susceptible isolates decreased for all antibiotics tested, and the median MIC increased regardless of which treatment the patient received (Table 2). In the 21 patients who had repeat cultures that grew *S. maltophilia*, the susceptibilities were reduced for SXT (96% to 71%), minocycline (95% to 57%), levofloxacin (82% to 29%), ceftazidime (49% to 33%), and ticarcillin-clavulanate (40% to 14%). Patients with pneumonia or bacteremia had the worst outcomes, with microbiological cure being the lowest and mortality being the highest in these patients (Table 3). Microbiological cure and clinical success rates were 50% and in-hospital mortality was 31% for patients with pneumonia, while microbiological cure was 40% and clinical success and in-hospital mortality were 33% for patients with bacteremia. These patients also had the highest rate of nonsusceptible isolates identified within 30 days of EOT (38 to 40%). There were no differences in clinical outcomes between patients who received levofloxacin and those who received ciprofloxacin (Table 3).

In univariate analysis, respiratory tract infection (*P* = 0.049), presence of CVC (*P* = 0.018), neutropenia at the time of culture (*P* = 0.002), a prednisone dose of ≥ 20 mg/day (*P* = 0.037), recent administration of chemotherapy (*P* = 0.0001), and admission to an ICU at the time of culture (*P* = 0.0001) were associated with increased in-hospital mortality. Admission to surgical service (*P* = 0.0001), hematological malignancy (*P* = 0.002), history of pulmonary disease (*P* = 0.034), polymicrobial infection (*P* = 0.043), coinfection with a Gram-negative organism (*P* = 0.016), and SSSI (*P* = 0.038) were associated with decreased in-hospital mortality. In the multivariate logistic regression model, admission to an ICU (odds ratio [OR], 8.2; 95% confidence interval [CI], 1.9

TABLE 1 Comparison of demographic characteristics of patients with *S. maltophilia* infection who received monotherapy with FQ or SXT

Patient characteristic	Value ^a						
	Overall (n = 98)	FQ (n = 63)		P value ^b	Total (n = 63)	SXT (n = 35)	P value ^c
	Levofloxacin (n = 48)	Ciprofloxacin (n = 15)					
Male gender	60 (61)	31 (65)	8 (53)	0.43	39 (62)	21 (60)	0.85
Age (yr) (mean ± SD)	73 ± 15	69 ± 14	71 ± 18	0.63	69 ± 15	73 ± 15	0.12
Underlying illness							
Major surgery	42 (43)	21 (44)	7 (47)	0.84	28 (44)	14 (40)	0.67
Malignancy (Solid Organ)	38 (39)	21 (44)	3 (20)	0.10	24 (38)	14 (40)	0.85
Coronary artery disease	37 (38)	19 (40)	7 (47)	0.63	26 (41)	11 (31)	0.34
Diabetes mellitus	35 (36)	19 (40)	7 (47)	0.63	26 (41)	9 (26)	0.12
Chronic kidney diseases/hemodialysis	25 (26)	14 (29)	4 (27)	1.0	16 (25)	9 (26)	0.97
Pulmonary disease	25 (26)	14 (29)	4 (27)	1.0	18 (29)	7 (20)	0.35
Congestive heart failure	24 (25)	13 (27)	6 (40)	0.35	19 (30)	5 (14)	0.08
Liver disease	9 (9)	4 (8)	3 (20)	0.34	7 (11)	2 (6)	0.38
Malignancy (hematological)	4 (4)	3 (6)	0 (0)	1.0	3 (5)	1 (3)	0.65
Immunosuppression							
Chemotherapy	19 (19)	11 (23)	1 (7)	0.26	12 (19)	7 (20)	0.91
Prednisone ≥ 20 mg/day	9 (9)	5 (10)	0 (0)	0.33	5 (8)	4 (11)	0.57
Solid organ/stem cell transplant	5 (6)	2 (4)	2 (13)	0.24	3 (6)	2 (7)	0.81
Neutropenia ^d	6 (6)	4 (8)	1 (7)	1.0	5 (8)	1 (3)	0.32
Tacrolimus or mycophenolate mofetil	5 (5)	2 (8)	2 (13)	0.24	4 (6)	1 (3)	0.45
Indwelling devices							
Genitourinary catheter	33 (34)	19 (40)	4 (27)	0.364	23 (37)	10 (29)	0.43
Mechanical ventilation	29 (30)	15 (31)	2 (13)	0.317	17 (27)	12 (34)	0.45
Central venous catheter	14 (14)	8 (17)	1 (7)	0.67	9 (14)	5 (14)	1.00
Intra-abdominal drain	7 (7)	1 (2)	0 (0)	1.0	1 (2)	6 (17)	<0.01
Chest tube	4 (4)	2 (4)	0 (0)	1.0	2 (3)	2 (6)	0.54
Ventriculoperitoneal shunt	4 (4)	1 (2)	1 (7)	0.422	2 (3)	2 (6)	0.54
Prior antibiotic use	82 (84)	44 (92)	10 (67)	0.03	54 (86)	28 (80)	0.46
Cephalosporins	48 (49)	31 (65)	5 (33)	0.03	36 (57)	12 (34)	0.03
Ceftazidime	1 (2)	1 (3)	0 (0)	1.0	1 (3)	0	1.0
Penicillins	47 (48)	22 (46)	7 (47)	0.96	29 (46)	18 (51)	0.61
Carbapenems	29 (30)	16 (33)	3 (20)	0.52	19 (30)	10 (29)	0.87
Aminoglycosides	17 (17)	11 (23)	3 (20)	1.0	14 (22)	3 (9)	0.09
Fluoroquinolones	17 (17)	7 (15)	2 (13)	1.0	9 (14)	8 (23)	0.28
Levofloxacin	7 (41)	2 (29)	0 (0)	1.0	2 (22)	5 (63)	0.04
Ciprofloxacin	7 (41)	4 (57)	2 (100)	0.622	6 (67)	1 (13)	0.22
Moxifloxacin	3 (18)	1 (2)	0 (0)	1.0	1 (11)	2 (25)	0.85
Tigecycline	6 (6)	4 (8)	1 (7)	1.0	5 (8)	1 (3)	0.42
Trimethoprim-sulfamethoxazole	5 (5)	3 (6)	1 (7)	1.0	4 (6)	1 (3)	0.65
Site of infection							
Pulmonary	55 (56)	32 (67)	6 (40)	0.07	38 (60)	17 (49)	0.26
Skin/skin structure	19 (19)	5 (10)	4 (27)	0.20	9 (14)	10 (29)	0.09
Urine	9 (9)	5 (10)	2 (13)	0.67	6 (10)	3 (9)	1.0
Intra-abdominal	9 (9)	2 (4)	3 (20)	0.08	5 (8)	4 (11)	0.72
Bacteremia	6 (6)	4 (8)	1 (7)	1.0	5 (8)	1 (3)	0.42
CRBSI ^e	3 (50)	2 (50)	1 (100)	0.56	3 (60)	0	0.55
Pulmonary	2 (33)	1 (25)	0 (0)	1.0	1 (20)	1 (100)	1.0
Skin/skin structure	1 (17)	1 (25)	0 (0)	1.0	1 (20)	0	1.0
Polymicrobial infection	75 (77)	31 (65)	12 (80)	0.35	53 (84)	22 (63)	0.02
Gram-negative organism	38 (39)	21 (44)	8 (53)	0.52	29 (46)	9 (26)	0.04
<i>Pseudomonas</i> spp.	10 (26)	5 (24)	3 (38)	0.38	8 (28)	2 (22)	0.49
<i>Escherichia coli</i>	5 (13)	4 (19)	1 (13)	1.0	5 (17)	0	0.09
<i>Enterobacter</i> spp.	7 (18)	5 (24)	1 (13)	1.0	6 (21)	1 (11)	0.42
<i>Serratia</i> spp.	3 (8)	1 (5)	0 (0)	1.0	1 (3)	2 (22)	0.29
<i>Proteus</i> spp.	3 (8)	0 (0)	1 (13)	0.24	1 (3)	2 (22)	0.29

(Continued on following page)

TABLE 1 (Continued)

Patient characteristic	Value ^a						
	Overall (n = 98)	FQ (n = 63)			Total (n = 63)	SXT (n = 35)	P value ^c
		Levofloxacin (n = 48)	Ciprofloxacin (n = 15)	P value ^b			
<i>Klebsiella</i> spp.	8 (21)	5 (24)	1 (13)	1.0	6 (21)	2 (22)	0.71
<i>Acinetobacter</i> spp.	7 (18)	4 (19)	2 (25)	0.62	6 (21)	1 (11)	0.42
Gram-positive organism	38 (39)	18 (38)	7 (47)	0.53	25 (40)	13 (37)	0.81
<i>Enterococcus</i> spp.	15 (39)	8 (44)	2 (29)	1.0	10 (40)	5 (38)	0.83
Methicillin-resistant <i>Staphylococcus aureus</i>	15 (39)	9 (50)	2 (29)	1.0	11 (44)	4 (31)	0.43
Methicillin-resistant <i>Staphylococcus epidermidis</i>	7 (18)	2 (11)	2 (29)	0.56	4 (10)	3 (23)	0.68
Methicillin-sensitive <i>S. aureus</i>	6 (16)	3 (17)	1 (14)	1.0	3 (12)	3 (23)	0.45
LOS ^f prior to culture (days) [median (IQR)]	5 (1–15)	6.5 (0–68)	3 (0–136)	0.76	6 (1–19)	4 (0–11)	0.79
LOS (days) [median (IQR)]	22 (12–38)	26.5 (4–149)	21 (5–166)	0.37	25 (15–37)	16 (8–42)	0.97
Days to treatment (days) [median (IQR)]	3 (2–4)	3 (0–36)	2 (0–14)	0.10	3 (2–4)	3 (2–5)	0.98
ICU admission at time of culture	23 (24)	16 (33)	1 (7)	0.05	17 (27)	6 (17)	0.27
CPIS ^g [median (IQR)]	4 (3–6)	4 (1–8)	3 (1–6)	0.16	4 (3–6)	4 (3–7)	0.89
CCI ^h [median (IQR)]	7 (5–8)	7 (0–13)	6 (1–9)	0.614	7 (5–8)	7 (4–8)	0.90

^a All values shown as number (percent), unless otherwise specified.

^b P value comparing patients who received levofloxacin to patients who received ciprofloxacin.

^c P value comparing patients who received trimethoprim-sulfamethoxazole to patients who received a fluoroquinolone.

^d Defined as an absolute neutrophil count below 500 cells/mm³.

^e CRBSI, catheter-related bloodstream infection.

^f LOS, length of stay.

^g CPIS, clinical pulmonary infection score; only calculated for pulmonary infections.

^h CCI, Charlson comorbidity index.

to 35; $P = 0.005$) and recent administration of chemotherapy (OR, 6.2; 95% CI, 1.12 to 34; $P = 0.037$) were independently associated with mortality. Variables that were independently associated with decreased mortality included admission to surgical service (OR, 0.17; 95% CI, 0.04 to 0.88), history of pulmonary disease (OR, 0.07; 95% CI, 0.01 to 0.83), polymicrobial infection (OR, 0.09; 95% CI, 0.02 to 0.45), and coinfection with a Gram-negative organism (OR, 0.14; 95% CI, 0.03 to 0.61).

TABLE 2 Comparison of susceptibility data for *S. maltophilia* isolates prior to and after initial treatment

Parameter	Value	
	Prior to initial treatment (n = 98)	After initial treatment (n = 21)
No. (%) of susceptible isolates/total		
Trimethoprim-sulfamethoxazole ^a	94/98 (96)	15/21 (71)
Minocycline	90/95 (95)	12/21 (57)
Levofloxacin ^b	79/96 (82)	6/21 (29)
Ceftazidime	47/95 (49)	7/21 (33)
Ticarcillin-clavulanate	38/96 (40)	3/21 (14)
Median MIC [μ g/ml (IQR)] [n]		
Trimethoprim-sulfamethoxazole ^c	20 (10–320) [91]	40 (20–100) [18]
Minocycline ^c	1 (0.1–48) [71]	3.5 (1–6) [14]
Levofloxacin ^d	1 (0.1–8), [72]	8 (3–8) [17]
Ticarcillin-clavulanate ^d	256 (0.4–256) [67]	256 (32–256) [15]
Ceftazidime ^d	24 (1–256) [67]	256 (16–256) [15]

^a Two of 7 (14%) isolates recovered following SXT monotherapy were resistant to SXT, and 2 of 5 (40%) were resistant to levofloxacin.

^b Ten of 14 (71%) isolates recovered following FQ monotherapy were resistant to levofloxacin, and 0 of 11 (0%) were resistant to SXT.

^c MIC according to Vitek 2 (bioMérieux).

^d MIC according to Etest (bioMérieux).

DISCUSSION

A microbiological cure rate of 63%, a clinical success rate of 55%, and an in-hospital mortality rate of 24% were identified for all patients with *S. maltophilia* infections treated with SXT or FQ monotherapy. Similar results were seen for patients regardless of whether they were treated with an FQ or SXT. Independent risk factors for mortality were admission to an ICU or recent administration of chemotherapy. Previously published mortality rates due to *S. maltophilia* vary widely, from 14 to 62% (6–13, 17). The variability in mortality rates may be due to differences in the types of infections included in each study. In a study by Wang et al., the all-cause mortality rate was 62% for patients with bacteremia, but only half of the deaths could be attributed to *S. maltophilia*, with the rest caused by underlying conditions (9), whereas in a study by Samonis et al., the all-cause mortality rate was 14%, with an infection-related mortality rate of only 4% (8). In the study by Samonis et al., the authors attributed the low mortality to the inclusion of non-critically ill patients, and the inclusion of patients with all infection types. Other studies identified mortality rates of 21 to 33%, which are consistent with the in-hospital mortality rate seen in this cohort (7–13). Similar to other studies, the cohort was not limited to bloodstream infections and included infections at other sites. Only 6 patients with bacteremia were included in the cohort, and 3 cases were related to a CVC. When patients with pneumonia or bacteremia were evaluated, higher in-hospital mortality rates of 31% (17/55) for pneumonia and 33% (2/6) for bacteremia were identified compared to 11% (4/37) for all other sites.

Along with the site of infection, clinical success may be influenced by the administration of adequate empirical antibiotic therapy. It is important to initiate appropriate antibiotics in most infections to minimize mortality, and inappropriate initial antimicrobial use in *S. maltophilia* infections can lead to higher mortality in bacteremic patients (12). In a prior study, 67% (8/13) of

TABLE 3 Clinical outcomes for patients with *S. maltophilia* infections who received monotherapy with FQ or SXT

Outcome	Value ^a						
	Overall (n = 98)	FQ (n = 63)			Total (n = 63)	SXT (n = 35)	P value ^c
		Levofloxacin (n = 48)	Ciprofloxacin (n = 15)	P value ^b			
Microbiological cure at EOT	36/57 (63)	18/30 (60)	5/7 (71)	0.69	23/37 (62)	13/20 (65)	0.83
Urine	8/8 (100)	5/5 (100)	1/1 (100)		6/6 (100)	2/2 (100)	
Skin/skin structure	6/7 (86)	2/3 (67)	1/1 (100)	1.0	3/4 (75)	3/3 (100)	1.00
Intra-abdominal	4/5 (80)	0/0 (0)	2/2 (100)		2/2 (100)	2/3 (67)	1.00
Pulmonary	16/32 (50)	10/19 (53)	0/2 (0)	0.48	10/21 (48)	6/11 (55)	0.71
Bacteremia	2/5 (40)	1/3 (33)	1/1 (100)	1.0	2/4 (50)	0/1 (0)	1.00
In-hospital mortality	23 (24)	15/48 (31)	1/15 (7)	0.09	16 (25)	7 (20)	0.55
Bacteremia	2/6 (33)	2/4 (50)	0/1 (0)	1.0	0/1 (0)	2/5 (40)	1.00
Pulmonary	17/55 (31)	11/32 (34)	1/6 (17)	0.64	12/38 (32)	5/17 (29)	0.87
Urine	2/9 (22)	1/5 (20)	0/1 (0)	1.0	1/6 (17)	1/3 (33)	1.00
Intra-abdominal	1/9 (11)	1/2 (50)	0/3 (0)	0.40	1/5 (20)	0/4 (0)	1.00
Skin/skin structure	1/19 (5)	0/5 (0)	0/4 (0)		0/9 (0)	1/10 (10)	1.00
30-day mortality	22/79 (28)	14/39 (36)	2/13 (15)	0.30	16/52 (31)	6/27 (22)	0.42
Pulmonary	18/45 (40)	11/27 (41)	2/5 (40)	1.0	13/32 (41)	5/13 (39)	0.89
Urine	2/7 (29)	1/4 (25)	0/1 (0)	1.0	1/5 (20)	1/2 (50)	1.00
Bacteremia	1/5 (20)	1/4 (25)	0/1 (0)	1.0	1/5 (20)		
Intra-abdominal	1/6 (17)	1/1 (100)	0/2 (0)	0.33	1/3 (33)	0/3 (0)	1.00
Skin/skin structure	0/16 (0)	0/3 (0)	0/4 (0)		0/7 (0)	0/9 (0)	
Clinical success at EOT	44/80 (55)	20/42 (48)	7/10 (70)	0.30	27/52 (52)	17/28 (61)	0.45
Urine	7/9 (78)	4/5 (80)	1/1 (100)	1.0	5/6 (83)	2/3 (67)	1.00
Skin/skin structure	9/14 (64)	1/2 (50)	3/3 (100)	0.40	4/5 (80)	5/9 (56)	0.58
Intra-abdominal	4/7 (57)	0/2 (0)	0/1 (0)		0/3 (0)	4/4 (100)	0.03
Pulmonary	22/44 (50)	14/29 (48)	2/4 (50)	1.0	16/33 (49)	6/11 (55)	0.73
Bacteremia	2/6 (33)	1/4 (25)	1/1 (100)	0.40	2/5 (40)	0/1 (0)	1.00
Nonsusceptible isolate within 30 days of EOT	15/57 (26)	9/30 (30)	2/7 (29)	1.0	11/37 (30)	4/20 (20)	0.43
Bacteremia	2/5 (40)	2/3 (67)	0/1 (0)	1.0	2/4 (50)	0/1	1.00
Pulmonary	12/32 (38)	6/19 (32)	2/2 (100)	0.13	8/21 (38)	4/11 (36)	1.00
Skin/skin structure	1/7 (14)	1/3 (33)	0/1 (0)	1.0	1/4 (25)	0/3 (0)	1.00
Urine	0/8 (0)	0/5 (0)	0/1 (0)		0/6 (0)	0/2 (0)	
Intra-abdominal	0/5 (0)	0/0 (0)	0/2 (0)		0/2 (0)	0/3 (0)	

^a All values shown as number/total (percent).

^b P value comparing patients who received levofloxacin to patients who received ciprofloxacin.

^c P value comparing patients who received trimethoprim-sulfamethoxazole to patients who received a fluoroquinolone.

patients who did not receive appropriate initial therapy for *S. maltophilia* bloodstream infections died compared to 17% (5/29) of those who received appropriate initial therapy (12). In this study, the median time to appropriate antibiotic therapy was 3 days, which is similar to prior studies (7). This may have contributed to the low success rate, although time to appropriate therapy was not a risk factor associated with increased mortality using multivariate analysis.

Failing to distinguish between colonization and infection with *S. maltophilia* may also influence clinical success (8). In studies that have compared patients who were colonized with *S. maltophilia* to those who were infected, mortality could not be directly attributed to *S. maltophilia* for patients who were only colonized with the organism (18). A limitation of this study is that it was not possible to distinguish between colonization and infection, although all of the patients were suspected to have an infection based on clinical documentation. It was also not possible to iden-

tify whether other organisms were contributing to the clinical outcome. A majority of patients had a polymicrobial infection that may have influenced the clinical outcome. The pathogenic role of *S. maltophilia* in polymicrobial infections makes it difficult to evaluate the contribution of *S. maltophilia* to the clinical symptoms in the infected patient (8, 10, 13). In this cohort, the presence of a polymicrobial infection was associated with decreased mortality in multivariate analysis, which could imply that the presence of other organisms may have contributed to the clinical outcome.

To our knowledge, this is the largest cohort study describing treatment outcomes of FQ monotherapy for *S. maltophilia* infections in the United States. Clinical data on the use of FQs for *S. maltophilia* are scarce, and most studies that evaluated clinical success included only patients treated with SXT or β -lactams (6–8, 10). Other studies reporting outcomes for alternative options for *S. maltophilia* infections did not evaluate outcomes based on individual drug classes, and studies that did evaluate treatment

with FQs are limited to case reports or the FQ was used in combination with other agents (6–13). In a systematic review, 20 of the 49 cases described treatment with ciprofloxacin for *S. maltophilia*. Only 8 patients received ciprofloxacin monotherapy, and 12 received another agent in combination with ciprofloxacin. All 8 patients who were treated with ciprofloxacin monotherapy were cured (6). In another study, only 6 patients received monotherapy with an FQ; however, the clinical effectiveness of FQ monotherapy could not be assessed because the authors did not evaluate individual regimens (8). Of the 98 patients in our cohort, 63 received an FQ alone as the primary treatment option, with a majority receiving levofloxacin. The clinical success rate and in-hospital mortality rate for FQs were 52% and 25%, respectively. The mortality rates for all patients and for those with pneumonia or bacteremia did not differ between SXT and FQ treatments.

This study evaluated only patients who received monotherapy for the treatment of *S. maltophilia*; however, combination therapy has been recommended for synergy and potential avoidance of resistance. Recommendations for the use of combination therapy for treatment of *S. maltophilia* are based on *in vitro* data and expert opinion (11). *In vitro* synergy has been reported with many combinations, and several studies suggest that emerging resistance could be potentially avoided by using combination therapy (10, 19–22). Muder et al. identified a mortality rate of 11% for those patients who received ≥ 2 classes of antibiotics to treat *S. maltophilia* compared to 31% in those who received only 1 antibiotic class (10). In this cohort, only patients who received monotherapy were evaluated, and a similar mortality rate was identified compared to previously mentioned studies, many of which included patients who received combination therapy (6, 8, 10). Although the mortality rates were similar to those in prior studies, 21 patients in this cohort who had repeat cultures that grew *S. maltophilia* had reduced susceptibilities for all antibiotics tested. With the knowledge that resistance may develop on monotherapy, the use of combination therapy needs to be further evaluated in order to determine whether it is effective in preventing the development of resistance. Since there are limited clinical data on the use of combination therapy, and *in vitro* synergy has not been shown with all antimicrobial combinations, it is not known whether the use of combination therapy will prevent resistance or whether it improves clinical outcomes.

Antimicrobial therapy for *S. maltophilia* infections is problematic, as isolates are usually resistant to multiple agents. Most *S. maltophilia* strains are resistant to aminoglycosides, extended-spectrum β -lactams, and 3rd-generation cephalosporins (5). Due to lack of clinical data, this study sought to evaluate the clinical outcomes of *S. maltophilia* infections and whether monotherapy with FQs can be used as an alternative to SXT. Fluoroquinolones had a success rate similar to that of SXT, although the success rates in both groups were relatively low. There were no statistically significant differences between patients who received SXT and patients who received FQs in terms of microbiological cure, clinical response, or mortality. Even though SXT is the drug of choice, treatment for *S. maltophilia* infection with SXT may not be possible due to resistance, allergies, toxicities, or drug shortages (23). Based on *in vitro* susceptibilities in this cohort, ticarcillin-clavulanate and ceftazidime do not appear to be viable options, as *in vitro* susceptibilities ranged from 40 to 49%. Minocycline and tigecycline may be potential options based on *in vitro* susceptibilities; however, clinical data to support their use are scarce (14).

Based on *in vitro* susceptibilities and current results, FQs may be an alternative option for use as monotherapy for the treatment of patients with *S. maltophilia* infections when SXT administration is not possible. Prospective studies are still needed to further compare the efficacies of FQs and SXT for the treatment of *S. maltophilia* infections and to evaluate whether minocycline or tigecycline is clinically effective against *S. maltophilia* and whether the use of combination therapy is beneficial in preventing the development of resistance.

ACKNOWLEDGMENTS

We have no conflicts of interest for this work. There was no pharmaceutical grant support for this study or outside influence on study concept, design, data analysis, and preparation of the manuscript.

REFERENCES

- Cervia JS, Ortolano GA, Canonica FP. 2008. Hospital tap water as a source of *Stenotrophomonas maltophilia* infection. *Clin. Infect. Dis.* 46: 1485–1487. <http://dx.doi.org/10.1086/587180>.
- Safdar A, Rolston KV. 2007. *Stenotrophomonas maltophilia*: changing spectrum of a serious bacterial pathogen in patients with cancer. *Clin. Infect. Dis.* 45:1602–1609. <http://dx.doi.org/10.1086/522998>.
- Metan G, Hayran M, Hascelik G, Uzun O. 2006. Which patient is a candidate for empirical therapy against *Stenotrophomonas maltophilia* bacteraemia? An analysis of associated risk factors in a tertiary care hospital. *Scand. J. Infect. Dis.* 38:527–531. <http://dx.doi.org/10.1080/00365540500452481>.
- Looney WJ, Narita M, Muhlemann K. 2009. *Stenotrophomonas maltophilia*: an emerging opportunist human pathogen. *Lancet Infect. Dis.* 9:312–323. [http://dx.doi.org/10.1016/S1473-3099\(09\)70083-0](http://dx.doi.org/10.1016/S1473-3099(09)70083-0).
- Nicodemo AC, Paez JI. 2007. Antimicrobial therapy for *Stenotrophomonas maltophilia* infections. *Eur. J. Clin. Microbiol. Infect. Dis.* 26:229–237. <http://dx.doi.org/10.1007/s10096-007-0279-3>.
- Falagas ME, Valkimadi PE, Huang YT, Matthaïou DK, Hsueh PR. 2008. Therapeutic options for *Stenotrophomonas maltophilia* infections beyond co-trimoxazole: a systematic review. *J. Antimicrob. Chemother.* 62: 889–894. <http://dx.doi.org/10.1093/jac/dkn301>.
- Czosnowski QA, Wood GC, Magnotti LJ, Croce MA, Swanson JM, Boucher BA, Fabian TC. 2011. Clinical and microbiologic outcomes in trauma patients treated for *Stenotrophomonas maltophilia* ventilator-associated pneumonia. *Pharmacotherapy* 31:338–345. <http://dx.doi.org/10.1592/phco.31.4.338>.
- Samonis G, Karageorgopoulos DE, Maraki S, Levis P, Dimopoulou D, Spernovasilis NA, Kofteridis DP, Falagas ME. 2012. *Stenotrophomonas maltophilia* infections in a general hospital: patient characteristics, antimicrobial susceptibility, and treatment outcome. *PLoS One* 7:e37375. <http://dx.doi.org/10.1371/journal.pone.0037375>.
- Wang WS, Liu CP, Lee CM, Huang FY. 2004. *Stenotrophomonas maltophilia* bacteremia in adults: four years' experience in a medical center in northern Taiwan. *J. Microbiol. Immunol. Infect.* 37:359–365.
- Muder RR, Harris AP, Muller S, Edmond M, Chow JW, Papadakis K, Wagener MW, Bodey GP, Steckelberg JM. 1996. Bacteremia due to *Stenotrophomonas (Xanthomonas) maltophilia*: a prospective, multi-center study of 91 episodes. *Clin. Infect. Dis.* 22:508–512. <http://dx.doi.org/10.1093/clinids/22.3.508>.
- Tsiodras S, Pittet D, Carmeli Y, Eliopoulos G, Boucher H, Harbarth S. 2000. Clinical implications of *Stenotrophomonas maltophilia* resistant to trimethoprim-sulfamethoxazole: a study of 69 patients at 2 university hospitals. *Scand. J. Infect. Dis.* 32:651–656. <http://dx.doi.org/10.1080/003655400459577>.
- Metan G, Uzun O. 2005. Impact of initial antimicrobial therapy in patients with bloodstream infections caused by *Stenotrophomonas maltophilia*. *Antimicrob. Agents Chemother.* 49:3980–3981. <http://dx.doi.org/10.1128/AAC.49.9.3980-3981.2005>.
- Kwa AL, Low JG, Lim TP, Leow PC, Kurup A, Tam VH. 2008. Independent predictors for mortality in patients with positive *Stenotrophomonas maltophilia* cultures. *Ann. Acad. Med. Singapore.* 37:826–830.
- Belvisi V, Fabietti P, Del Borgo C, Marocco R, Di Vincenzo E, Soscia F, Mastroianni CM. 2009. Successful treatment of *Stenotrophomonas*

- maltophilia soft tissue infection with tigecycline: a case report. *J. Chemother.* 21:367–368.
15. Weiss K, Restieri C, De Carolis E, Laverdiere M, Guay H. 2000. Comparative activity of new quinolones against 326 clinical isolates of *Stenotrophomonas maltophilia*. *J. Antimicrob. Chemother.* 45:363–365. <http://dx.doi.org/10.1093/jac/45.3.363>.
 16. Horan TC, Andrus M, Dudeck MA. 2008. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am. J. Infect. Control* 36:309–332. <http://dx.doi.org/10.1016/j.ajic.2008.03.002>.
 17. Tseng CC, Fang WF, Huang KT, Chang PW, Tu ML, Shiang YP, Douglas IS, Lin MC. 2009. Risk factors for mortality in patients with nosocomial *Stenotrophomonas maltophilia* pneumonia. *Infect. Control Hosp. Epidemiol.* 30:1193–1202. <http://dx.doi.org/10.1086/648455>.
 18. Villarino ME, Stevens LE, Schable B, Mayers G, Miller JM, Burke JP, Jarvis WR. 1992. Risk factors for epidemic *Xanthomonas maltophilia* infection/colonization in intensive care unit patients. *Infect. Control Hosp. Epidemiol.* 13:201–206. <http://dx.doi.org/10.1086/646510>.
 19. Bonfiglio G, Cascone C, Azzarelli C, Cafiso V, Marchetti F, Stefani S. 2000. Levofloxacin in vitro activity and time-kill evaluation of *Stenotrophomonas maltophilia* clinical isolates. *J. Antimicrob. Chemother.* 45:115–117. <http://dx.doi.org/10.1093/jac/45.1.115>.
 20. Vartivarian S, Anaissie E, Bodey G, Sprigg H, Rolston K. 1994. A changing pattern of susceptibility of *Xanthomonas maltophilia* to antimicrobial agents: implications for therapy. *Antimicrob. Agents Chemother.* 38:624–627. <http://dx.doi.org/10.1128/AAC.38.3.624>.
 21. Munoz JL, Garcia MI, Munoz S, Leal S, Fajardo M, Garcia-Rodriguez JA. 1996. Activity of trimethoprim/sulfamethoxazole plus polymyxin B against multidrug-resistant *Stenotrophomonas maltophilia*. *Eur. J. Clin. Microbiol. Infect. Dis.* 15:879–882. <http://dx.doi.org/10.1007/BF01691222>.
 22. San Gabriel P, Zhou J, Tabibi S, Chen Y, Trauzzi M, Saiman L. 2004. Antimicrobial susceptibility and synergy studies of *Stenotrophomonas maltophilia* isolates from patients with cystic fibrosis. *Antimicrob. Agents Chemother.* 48:168–171. <http://dx.doi.org/10.1128/AAC.48.1.168-171.2004>.
 23. Toleman MA, Bennett PM, Bennett DM, Jones RN, Walsh TR. 2007. Global emergence of trimethoprim/sulfamethoxazole resistance in *Stenotrophomonas maltophilia* mediated by acquisition of sul genes. *Emerg. Infect. Dis.* 13:559–565. <http://dx.doi.org/10.3201/eid1304.061378>.