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MAJOR ARTICLE

Trimethoprim-Sulfamethoxazole Versus Levofloxacin for *Stenotrophomonas maltophilia* Infections: A Retrospective Comparative Effectiveness Study of Electronic Health Records from 154 US Hospitals

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Background. Trimethoprim-sulfamethoxazole (TMP-SMX) is considered first-line therapy for *Stenotrophomonas maltophilia* infections based on observational data from small studies. Levofloxacin has emerged as a popular alternative due to tolerability concerns related to TMP-SMX. Data comparing levofloxacin to TMP-SMX as targeted therapy are lacking.

Methods. Adult inpatient encounters January 2005 through December 2017 with growth of *S maltophilia* in blood and/or lower respiratory cultures were identified in the Cerner Healthfacts database. Patients included received targeted therapy with either levofloxacin or TMP-SMX. Overlap weighting was used followed by downstream weighted regression. The primary outcome was adjusted odds ratio (aOR) for in-hospital mortality or discharge to hospice. The secondary outcome was number of days from index *S maltophilia* culture to hospital discharge.

Results. Among 1581 patients with *S maltophilia* infections, levofloxacin (n = 823) displayed statistically similar mortality risk (aOR, 0.76 [95% confidence interval {CI}, .58–1.01]; $P = .06$) compared to TMP-SMX (n = 758). Levofloxacin (vs TMP-SMX) use was associated with a lower aOR of death in patients with lower respiratory tract infection (n = 1452) (aOR, 0.73 [95% CI, .54–.98]; $P = .03$) and if initiated empirically (n = 89) (aOR, 0.16 [95% CI, .03–.95]; $P = .04$). The levofloxacin cohort had fewer hospital days between index culture collection and discharge (weighted median [interquartile range], 7 [4–13] vs 9 [6–16] days; $P < .0001$).

Conclusions. Based on observational evidence, levofloxacin is a reasonable alternative to TMP-SMX for the treatment of bloodstream and lower respiratory tract infections caused by *S maltophilia*.

Keywords. levofloxacin; *Stenotrophomonas maltophilia*; TMP-SMX; trimethoprim-sulfamethoxazole.

Stenotrophomonas maltophilia is a ubiquitous, gram-negative organism increasingly recognized as an antibiotic-resistant pathogen that threatens hospitalized patients globally [1]. Though not particularly virulent, *S maltophilia* has proven itself a formidable pathogen in the setting of intensive healthcare contact, immunosuppression, and other comorbid conditions [2, 3]. It is of particular concern in the hospital setting resulting from its propensity to form biofilms and its survival in nutrient-poor environments [4]. Infections owing to this organism have increased significantly in recent years due in part to growing populations with these risk factors [5]. Infections caused by *S maltophilia* are often difficult to treat due to a variety of intrinsic and acquired resistance traits that evade traditional empiric antibiotic regimens [2, 3, 6, 7]. *Stenotrophomonas maltophilia* can cause a variety of serious infections in the human host; most notably, it is associated with lower respiratory tract infections (LRTIs) and bloodstream infections (BSIs). With limited targeted therapy options, this organism continues to pose a substantial mortality burden [4, 6, 8]. Thus, a better understanding of the optimal treatment of *S maltophilia* is needed.

Traditionally, the treatment of choice for *S maltophilia* infection is trimethoprim-sulfamethoxazole (TMP-SMX), based predominantly on in vitro studies and case series [4, 7, 9, 10]. However, TMP-SMX is often associated with treatment-limiting toxicities including renal and hepatic injury, fluid and

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electrolyte derangements, hemolysis (ie, glucose 6–phosphate dehydrogenase deficiency), bone marrow suppression, and hypersensitivity reactions [11, 12]. Additionally, *S maltophilia* isolates exhibiting resistance to TMP-SMX are increasingly reported [13–16]. Levofloxacin has emerged as a popular alternative for *S maltophilia* infections based on in vitro susceptibility data, available breakpoint recommendations, and clinician familiarity [17–21]. However, levofloxacin also has a variety of adverse effects, including cardiac conduction abnormalities, tendinopathy, gastrointestinal intolerance, and increased risk of *Clostridioides difficile* infection (CDI) [22, 23]. More *S maltophilia* isolates tend to be intrinsically resistant to levofloxacin than TMP-SMX, making it less often a targeted treatment option compared to TMP-SMX [10, 24]. Furthermore, prior fluoroquinolone use has been associated with resistance to levofloxacin [25]. Despite the clinical need, there is no randomized controlled trial (RCT) to date that compares TMP-SMX and levofloxacin for *S maltophilia* infections. Thus, the optimal treatment of serious *S maltophilia* infection is unknown. In the current study, we used a large electronic health record database to conduct a retrospective comparative effectiveness study of levofloxacin vs TMP-SMX for BSIs and LRTIs due to *S maltophilia*.

METHODS

Study Design and Case Selection

The Cerner Healthfacts database was queried for unique adult (≥18 years) inpatient encounters admitted between 1 January 2005 and 31 December 2017 that recorded growth of *S maltophilia* in ≥1 blood or lower respiratory tract culture. The latter included sputum, tracheal aspirate, bronchoalveolar lavage, and protected bronchial brush washings. One initial encounter per patient was included for analysis. Patients had to have been treated with either TMP-SMX or levofloxacin and were excluded if they received any other antimicrobial with known in vitro activity against *S maltophilia*. Antimicrobials that fit this exclusion criteria were erythromycin, moxifloxacin, ciprofloxacin, minocycline, tigecycline, doxycycline, eravacycline, ceftazidime, cefepime, ticarcillin-clavulanate, cefiderocol, colistin, and chloramphenicol (Supplementary Table 1). Patients who received both levofloxacin and TMP-SMX (either concomitantly or sequentially as empiric vs targeted therapy and vice versa) were excluded, as were patients with cystic fibrosis (given their unique epidemiology and risk profile) [26] and where the isolate was resistant to the antibiotic initially selected upon speciation (eg, if TMP-SMX was given during treatment window and isolate speciated resistant to TMP-SMX, patient was excluded; Supplementary Table 2). Henceforth, assuming day 0 as the day index culture resulted positive, empiric therapy was defined as occurring on day –2 or day –1, and targeted therapy was defined as occurring on or between day 0 to day +7 (Supplementary Table 3).

Patient Consent Statement

Given that the study exclusively used deidentified data, it was deemed not to require patient consent and was deemed exempt from ethics board review at the National Institutes of Health (NIH) Clinical Center, based on the policy of the NIH Office of Human Subjects Research Protections, under the revised Common Rule.

Statistical Analysis

Analyses were prespecified unless explicitly reported as post hoc. The study protocol and statistical analysis plan were published online on ClinicalTrials.gov (identifier NCT04639817) prior to conducting analyses. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines for reporting observational studies were followed [27]. Baseline characteristics were compared between the 2 groups using χ^2 tests for categorical variables and *t* test or Wilcoxon rank-sum test for continuous variables.

A propensity score was generated using clinically relevant patient, infection, treatment, and center-related variables. These include age, sex, immunocompromised status (Supplementary Table 4), baseline Sequential Organ Failure Assessment (SOFA) score (on day index culture was collected; Supplementary Table 5), Elixhauser comorbidity index, culture site, polymicrobial infection (Supplementary Methods and Supplementary Tables 6 and 7), intensive care unit (ICU) stay (between 1 day before and up to 2 days following the day of culture sampling), mechanical ventilation, vasopressor use, and year range, as well as hospital factors: academic status, urban/rural qualification, geographic region, and bed capacity. To ensure balance between the 2 groups, we used overlap weighting as implemented in R (version 4.0.3) package PSweight (version 1.1.2) [28].

Overlap Weighting

Overlap weighting is a relatively new statistical technique first described by Li et al in 2018 that allows for exact balance between groups and attempts to simulate randomization [29]. Unlike propensity matching, which invariably results in excluding some individuals by assigning an artificial cutoff for trimming, and inverse probability weighting, which tends to assign considerable weight to outliers, overlap weighting uses the propensity score to assign weights based on the probability that a given patient in 1 treatment group belongs to the other treatment group. This results in conscious underweighting of outliers, such that the results are based predominantly on those in whom the decision to use levofloxacin vs TMP-SMX may have been more discretionary than confounded by indication [30].

The primary outcome for analysis was in-hospital mortality or discharge to hospice. This was analyzed using weighted

logistic regression and presented as an adjusted odds ratio (aOR). To capture morbidity potentially attributable to treatment choice, the number of days from index *S maltophilia* culture to discharge was selected as the secondary outcome, where mortality was censored at the longest length of stay and analyzed using weighted Cox regression.

Predefined subgroups for analysis include site of infection (LRTI, BSI), SOFA score (high ≥2 or low <2) and mechanical ventilation restricted to within ±3 days of culture collection. Sensitivity analyses were performed with and without polymicrobial culture growth, polymicrobial growth additionally treated with non–*S maltophilia*–active antibiotic(s), receipt of empiric therapy, empiric therapy not received, non–present-on-admission diagnosis coding for pneumonia, and imputed susceptibility.

Upon discovery that the median time from admission to culture was significantly different between study groups (weighted median, 4 [interquartile range {IQR}, 1–11] days for TMP-SMX vs 2 [IQR, 0–9] days for the levofloxacin group; $P < .0001$) and could possibly introduce immortal time bias, a post hoc analysis was performed including this variable in risk adjustment using weighted logistic regression. All statistical analyses were performed using R (version 4.0.3), package PSweight (version 1.1.2) or SAS (version 9.4) software.

RESULTS

Between 2005 and 2017, there were 14 930 unique inpatients at 154 hospitals in the United States with any culture positive for *S maltophilia* in the database. After applying selection criteria (Figure 1), 1581 assessable inpatients were identified: 823 (52%) inpatients in the levofloxacin cohort and 758 (48%) in the TMP-SMX cohort.

Baseline Characteristics

Baseline characteristics are presented in Table 1. Patients in the TMP-SMX (vs levofloxacin) cohort were younger (median age, 60 [IQR, 31–72] years vs 66 [IQR, 53–76] years; $P < .0001$), more likely to be mechanically ventilated at any time during their admission (38.7% [293/758] vs 31.2% [257/823]; $P = .002$), and more likely to have an ICU stay (33.5% [254/758] vs 28.8% [237/823]; $P = .04$) during their hospitalization. Proportions of mechanically ventilated patients were similar, at 10.3% (78/758; $P = .86$) in the TMP-SMX group and 10.6% (87/823) in the levofloxacin group within the predefined window of ±3 days around culture sampling (Supplementary Table 8). Patients in the levofloxacin cohort, compared with TMP-SMX, displayed a greater frequency of *S maltophilia* bacteremia (12.0% [99/823] vs 8.4% [64/758], respectively; $P = .02$) and were more likely to have received concordant empiric therapy (10.0% [82/823] vs 0.9% [7/758]; $P < .0001$). In our study, 41.6% (658/1581) of overall patients (41.7% [343/823] in the levofloxacin cohort vs 41.6% [315/758] in the TMP-SMX cohort) had a polymicrobial index culture. Notably, 39.9% (65/163) with BSIs had a polymicrobial index culture that included *S maltophilia*. Other characteristics were comparable in the levofloxacin vs TMP-SMX cohorts, including SOFA score (median, 1 [IQR, 0–4] vs 1 [IQR, 0–4]) and Elixhauser comorbidity index (median, 2 [IQR, 0–4] vs 1 [IQR, 0–4]). After overlap weighting, the mean standard difference at each variable assessed was zero (Supplementary Figure 1).

Primary Outcome

Unadjusted mortality for the study cohort was 16.4% (259/1581) overall, 14.1% (23/163) for patients with BSI, and 19.5% (60/307) for patients with LRTI due to *S maltophilia*. Approximately 15% (125/823) of patients in the levofloxacin group and 17.7% (134/758) of those in the TMP-SMX group died. Levofloxacin use was associated with a nonsignificant trend toward lower aOR of death as compared with TMP-SMX (aOR, 0.76 [95% CI, .58–1.01]; $P = .057$) (Figure 2). A statistically significant lower aOR of death associated with levofloxacin (vs TMP-SMX) was noted in the prespecified subgroups of patients who had an LRTI (n = 1452) (aOR, 0.73 [95% CI, .54–.98]; $P = .03$), nonventilated patients (n = 1456) (aOR, 0.74 [95% CI, .54–.997]; $P = .048$), and those in whom the agent was initiated empirically (n = 89) (aOR, 0.16 [95% CI, .03–.95]; $P = .04$). All other subgroup and sensitivity analyses yielded similar impacts of both agents on mortality risk (Figure 2).

Secondary Outcome

Compared to the TMP-SMX cohort, the levofloxacin cohort had fewer hospital days between index culture draw and discharge (weighted median, 7 [IQR, 4–13] days vs 9 [IQR, 6–16] days; $P < .0001$) (Figure 3). The hazard ratio (HR) of discharge alive in the levofloxacin group compared with the TMP-SMX group was 1.28 (95% CI, 1.15–1.43]; $P < .0001$), suggesting a statistically significant shorter length of stay. Secondary outcome findings were also fairly consistent across subgroups and sensitivity analyses (Figure 3), except for patients with BSI, those on mechanical ventilation, and those with polymicrobial infection having received therapy, in whom there was no statistically significant difference in HR for discharge (HR, 0.99 [95% CI, .70–1.39], $P = .96$; HR, 1.04 [95% CI, .72–1.51], $P = .84$; and HR, 1.02 [95% CI, .79–1.31], $P = .89$, respectively).

Post Hoc Analysis

After adjusting for time to culture as a continuous variable to mitigate immortal time bias, the OR of death for levofloxacin vs TMP-SMX was found to be 0.82 ([95% CI, .62–1.09]; $P = .17$). The HR for discharge alive in the levofloxacin group compared with the TMP-SMX group was 1.22 (95% CI, 1.09–1.37]; $P = .0004$). These results are generally consistent with findings from the initial planned analysis with 2 exceptions: The OR of

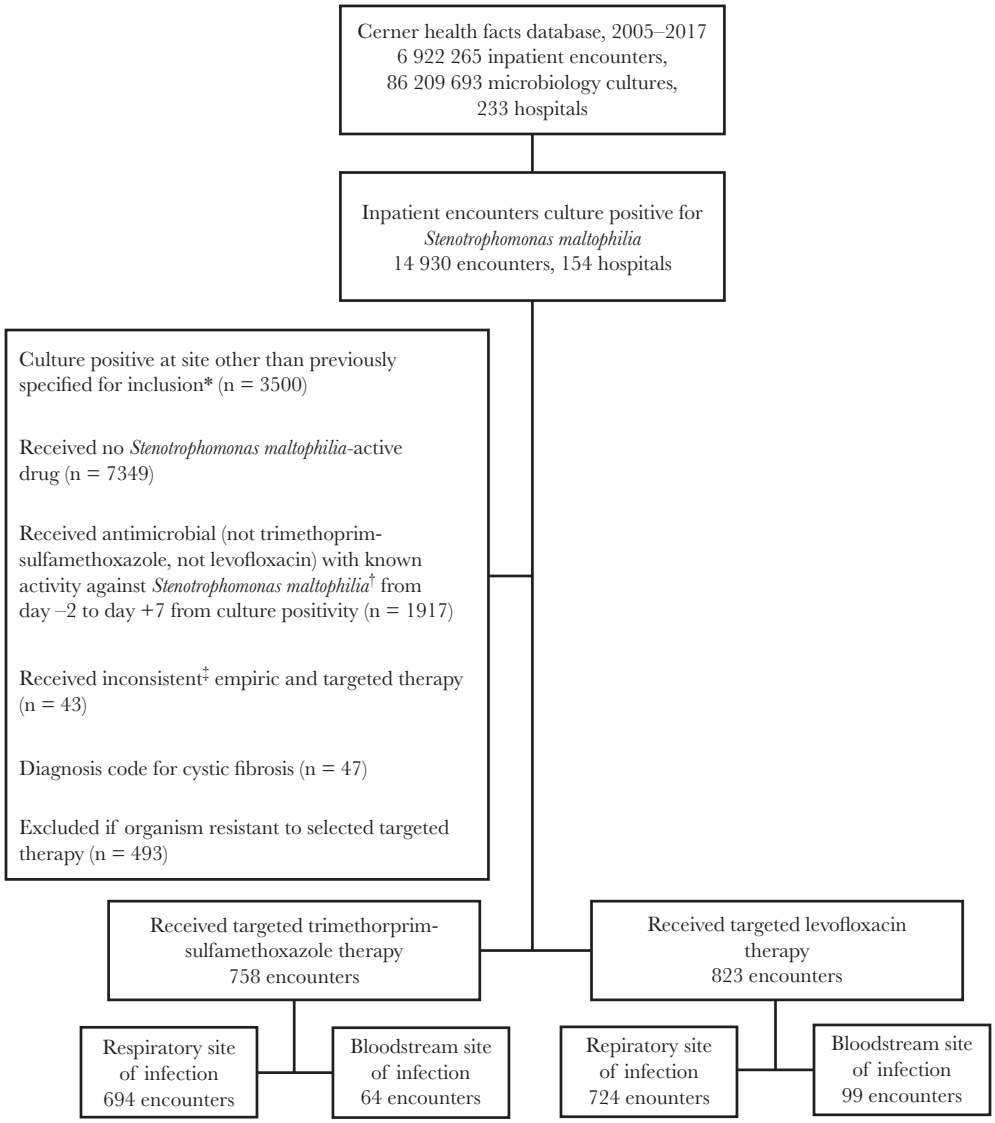

Figure 1. Case selection flowchart. Depiction of case selection process, including cases filtered in the data for exclusions. *Included clinical culture sites: blood culture, bronchoalveolar lavage, protected bronchial brush washing, sputum culture, and tracheal aspirate. Patients with bloodstream and respiratory infection due to *Stenotrophomonas maltophilia* were counted in the bloodstream site of infection category. †Antimicrobials with activity against *Stenotrophomonas* 2 days prior to and 7 days after culture positivity were excluded. Known *Stenotrophomonas*-active agents that were excluded are erythromycin, moxifloxacin, ciprofloxacin, minocycline, tigecycline, doxycycline, eravacycline, ceftazidime, cefepime, ticarcillin-clavulanate, cefiderocol, colistin, and chloramphenicol. ‡Defined as receiving levofloxacin as empiric therapy (day –2 to –1 from culture positivity) and trimethoprim-sulfamethoxazole as targeted therapy and vice versa.

death for levofloxacin vs TMP-SMX was 0.79 (95% CI, .58–1.06; $P = .12$) for the subgroup of patients with LRTI and 0.17 (95% CI, .02–1.36; $P = .09$) for those having received concordant therapy. Although the findings of these 2 subgroups were consistent in directionality with the corresponding prespecified analyses, adjustment for time to culture rendered estimates as not statistically significant. Post hoc analyses are presented in Supplementary Figure 2.

DISCUSSION

Our study of 1581 patients from 154 US hospitals represents the largest retrospective cohort analysis thus far comparing the effectiveness of levofloxacin vs TMP-SMX as targeted therapy for *S maltophilia* bloodstream and lower respiratory tract infections. Overall, we found comparable mortality risk with the use of either levofloxacin or TMP-SMX for these serious *S maltophilia* infections. Furthermore, patients treated with levofloxacin in the prespecified subgroup of those with pneumonia appeared to display greater survival compared to TMP-SMX and were discharged sooner. In vitro–active empiric therapy appeared to be associated with a decreased risk of death overall.

TMP-SMX is considered the first-line agent for *S maltophilia* largely due to its in vitro susceptibility profile [10, 24, 31] and observational studies supporting its use [17, 20, 21, 32, 33]. In

Table 1. Baseline Characteristics for Patients With *Stenotrophomonas maltophilia* Infection

Characteristic	Levofloxacin (n = 823)	TMP -SMX (n = 758)
Patient-level factors		
Admission year		
2005–2010	204 (24.8)	197 (26.0)
2011–2013	208 (25.3)	208 (27.4)
2014–2015	234 (28.4)	192 (25.3)
2016–2017	177 (21.5)	161 (21.2)
Age, y		
18–44	138 (16.8)	239 (31.5)
45–64	247 (30.0)	203 (26.8)
65–74	215 (26.1)	174 (23.0)
≥75	223 (27.1)	142 (18.7)
Sex		
Female	362 (44.0)	327 (43.1)
Male	461 (56.0)	431 (56.9)
Race		
Black	116 (14.1)	143 (18.9)
White	637 (77.4)	505 (66.6)
Other[a]	70 (8.5)	110 (14.5)
Infection site		
Blood[b]	99 (12.0)	64 (8.4)
Respiratory	724 (88.0)	694 (91.6)
SOFA score[c], median (IQR)	1.0 (0.0–4.0)	2.0 (0.0–4.0)
Mechanical ventilation[d]	87 (10.6)	78 (10.3)
Polymicrobial infection	343 (41.7)	315 (41.6)
Polymicrobial infection receiving treatment	165 (20.0)	178 (23.5)
ICU admission[e]	215 (26.1)	237 (31.3)
Therapy initiated empirically	82 (10.0)	7 (0.9)
Pneumonia diagnosis[f]	166 (20.2)	141 (18.6)
Immunocompromised	8 (1.0)	13 (1.7)
Vasopressor administration[g]	89 (10.8)	87 (11.5)
Elixhauser score, median (IQR)	2.0 (0.0–4.0)	2.0 (0.0–5.0)
Length of stay, median (IQR)	10.0 (5.0–21.0)	17.0 (9.0–31.8)
Discharge to hospice	38 (4.6)	26 (3.4)
In-hospital mortality	87 (10.6)	108 (14.2)
Total mortality	125 (15.2)	134 (17.7)
Hospital-level factors		
Teaching facility	506 (63.8)	473 (67.4)
Bed capacity		
>100	81 (9.8)	90 (11.9)
100–199	142 (17.3)	81 (10.7)
200–299	145 (17.6)	129 (17.0)
300–499	292 (35.5)	262 (34.6)
≥500	163 (19.8)	196 (25.9)
Urban location	718 (87.2)	605 (79.8)
Census region		
Midwest	181 (22.0)	196 (25.9)
Northeast	156 (19.0)	146 (19.3)
South	350 (42.5)	278 (36.7)
West	136 (16.5)	138 (18.2)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ICU, intensive care unit; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment; TMP-SMX, trimethoprim-sulfamethoxazole.

[a]Includes Asian, Pacific Islander, biracial, Hispanic, Native American, other, and unknown.

[b]Encounters with both blood and respiratory sites of infection were categorized as blood infections.

[c]On day index culture was collected.

[d]Day –1 to +2 where culture is collected.

[e]Culture was drawn in ICU setting.

[f]Presence of the *International Classification of Diseases (ICD), Ninth Revision* diagnosis codes 481, 485, 486, 514; or *ICD, Tenth Revision* diagnosis codes J18.0, J18.1, J18.2, J18.8, J18.9.

[g]Day –1 to day +2 day index culture was collected.

Levofloxacin versus TMP/SMX		Unadjusted data		Adjusted‡ data	
Groups	**No.**	**OR† (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Primary cohort (bloodstream and respiratory infection)	1581	0.83 (.63 –1.10)	.20	0.76 (.58 –1.01)	.057
Bloodstream infection	169	1.25 (.46–3.64)	.82	1.18 (.47 –3.02)	.72
Respiratory infection	1452	0.81 (.60–1.08)	.15	0.73 (.54 –.98)	.03
SOFA score <2	843	0.83 (.49–1.39)	.46	0.71 (.44 –1.15)	.17
SOFA score ≥2	738	0.88 (.62–1.25)	.49	0.82 (.57 –1.16)	.26
No mechanical ventilation	1456	0.76 (.56–1.02)	.064	0.74 (.54 –1.00)	.048
Mechanical ventilation	165	1.44 (.67–3.16)	.37	0.94 (.45 –1.97)	.86
Polymicrobial infection	658	0.90 (.59–1.37)	.68	0.80 (.52 –1.23)	.31
Polymicrobial infection receiving therapy*	343	1.19 (.65–2.18)	.57	1.16 (.63 –2.15)	.63
Susceptibility results available	1417	0.86 (.65–1.15)	.32	0.81 (.60 –1.08)	.15
Indicators of pneumonia	307	0.69 (.38–1.27)	.25	0.60 (.33 –1.08)	.09
Therapy initiated empirically	89	0.28 (.042–2.12)	.12	0.16 (.03 –.95)	.04

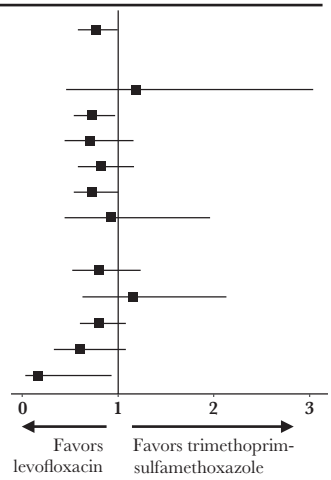

Figure 2. Odds ratios of mortality for levofloxacin vs trimethoprim-sulfamethoxazole targeted therapy among primary cohort and subpopulations of interest. Forest plot of boxes depicting adjusted odds ratio with 95% confidence intervals shown as horizontal lines. *Excluding drugs with known activity against *S maltophilia* other than Trimethoprim-sulfamethoxazole and Levofloxacin (Appendix Table 4). †Unadjusted data calculated using Fisher's exact test. ‡Adjusted values were calculated using logistic regression after controlling for baseline patient and hospital level factors. Clinically relevant sub-populations were also analyzed for potential disparate impacts on mortality. Abbreviations: CI, confidence interval; OR, odds ratio; SOFA, Sequential Organ Failure Assessment; TMP-SMX, trimethoprim-sulfamethoxazole.

the absence of RCT data, clinicians seek alternative agents for managing *S maltophilia* due to tolerability limitations of TMP-SMX, especially among patient populations uniquely susceptible to this pathogen (eg, neutropenic, critically ill). Our findings complement a previous meta-analysis [32] of 7 retrospective cohort and 7 case-control studies (pooled n = 663 patients) that also suggested comparable survival rates for both agents. However, the meta-analysis pooled unadjusted ORs from relatively small studies (range, 1–35 patients for levofloxacin and 2–68 patients for TMP-SMX) that did not account for confounding by indication—a major obstacle in nonrandomized comparisons of the effectiveness of alternatives to an established

Levofloxacin versus TMP/SMX			
Groups	**No.**	**Hazard ratio (95% CI)**	***P* Value**
Primary cohort (bloodstream and respiratory infection)	1581	1.28 (1.15–1.43)	<.0001
Bloodstream infection	169	0.99 (.70–1.39)	.96
Respiratory infection	1452	1.32 (1.17–1.49)	<.0001
SOFA score <2	843	1.38 (1.18–1.62)	<.0001
SOFA score ≥2	738	1.19 (1.01–1.39)	.04
No mechanical ventilation	1456	1.32 (1.17–1.48)	<.0001
Mechanical ventilation	165	1.04 (.72–1.51)	.84
Polymicrobial infection	658	1.28 (1.07–1.53)	.006
Polymicrobial infection receiving therapy*	343	1.02 (.79–1.31)	.89
Susceptibility results available	1417		
Indicators of pneumonia	307	1.38 (1.07–1.77)	.01
Therapy initiated empirically	89	2.85 (.73–11.18)	.13

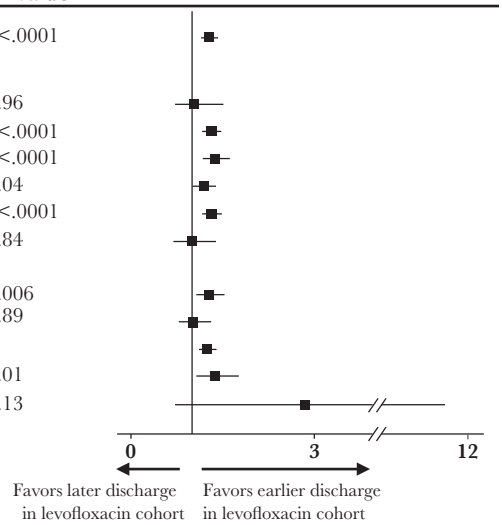

Figure 3. Hazard ratios of discharge for levofloxacin vs trimethoprim-sulfamethoxazole (TMP-SMX) targeted therapy among primary cohort and subpopulations of interest. Forest plot of boxes depicting hazard ratios with 95% confidence intervals shown as horizontal lines. A higher hazard ratio of discharge for the levofloxacin cohort vs TMP-SMX cohort correlates with a shorter length of stay for the levofloxacin cohort, since this information is presented as a risk of being discharged. Abbreviations: CI, confidence interval; SOFA, Sequential Organ Failure Assessment; TMP-SMX, trimethoprim-sulfamethoxazole. *Excluding drugs with known activity against *S maltophilia* other than Trimethoprim-sulfamethoxazole and Levofloxacin (Appendix Table 4).

treatment standard—thus impeding inferences of comparative effectiveness.

Our study displays several strengths over previous studies and provides incremental evidence on the topic. First, our study provides greater statistical power than previous studies in inferring that the 2 agents are likely comparably effective against *S maltophilia* overall. Second, our study applied overlap weighting that resulted in excellent covariate balance and applied weighted regression to mitigate residual confounding. Third, our findings are robust to several sensitivity analyses. We used both monomicrobial and polymicrobial *S maltophilia* infections in our primary analysis; *S maltophilia* is often part of a polymicrobial infection, as demonstrated in our study (41.5%) and other studies (range, 33%–70%) [19, 34, 35]. Our findings were similar upon limiting the analysis to polymicrobial infections treated with agents not active against *S maltophilia*, further enhancing internal and external validity of our findings. We imputed susceptibility when these data were not reported for study agents (in approximately 10% of cases) and results were similar with or without inclusion of imputed susceptibility results.

Our study indicates a growing comfort level among clinicians in the use of levofloxacin to treat *S maltophilia* infection in the real-world setting. Despite demonstration of comparable efficacy, there was a nonsignificant trend toward favoring levofloxacin in the primary analysis. This signal was likely driven by the potential superiority of levofloxacin over TMP-SMX for pneumonia. The latter is hypothesis generating and prospective studies are needed to confirm these findings. However, pharmacokinetic/pharmacodynamic properties benefiting levofloxacin over TMP-SMX, such as a higher concentration in epithelial lining fluid, quicker time-to-peak serum concentration, bactericidality, and greater bioavailability of the oral formulation, add biologic plausibility to our observations [11, 36–39]. The estimate for the effect of TMP-SMX (vs levofloxacin) in BSIs is uninterpretable in the context of a wide CI. Furthermore, we found a statistically significant decrease in mortality risk when *S maltophilia*–active therapy was initiated empirically. Given the 10-fold greater empiric use of levofloxacin (vs TMP-SMX), this finding does not so much as indicate which agent is more effective for empiric use, but rather that earlier initiation of active therapy improves outcomes in *S maltophilia* infections, as previously suggested [33, 40]. No difference in mortality was found in the subgroup that did not receive empiric therapy, further corroborating the comparable effectiveness of levofloxacin and TMP-SMX for *S maltophilia* infections. As the nationwide uptake and reliability of rapid molecular diagnostics grows over time, an earlier diagnosis is likely to improve survival rates for *S maltophilia* infection. The overall shorter length of stay observed in the levofloxacin group, although statistically significant, is perhaps less clinically relevant, as there are many social and clinical explanations that could account for a 2-day difference in length of stay. Nevertheless, the results support the use of levofloxacin as an alternative standard of care for *S maltophilia* infections.

Our study has important limitations. Unmeasured confounding may still exist, and adequacy of source control could not be gauged; however, this bias is likely to be nondifferential. Despite use of a comprehensive definition for immunosuppression, billing codes may have limited our ability to capture the sum of immunosuppressed hosts. Our study does not address combination therapy, a treatment modality commonly used for multidrug-resistant gram-negative pathogens. Notably, levofloxacin is not the only alternative to TMP-SMX. Minocycline and the recently Food and Drug Administration–approved cefiderocol both appear to have in vitro activity against >99% of *S maltophilia* isolates [24, 41]. As such, the treatment paradigm may shift with additional efficacy data. Development of resistance under treatment, a concern with levofloxacin use in particular, was not addressed. Information required to adequately assess key tolerability outcomes (eg, urine output for acute kidney injury, stool characteristics for CDI) precluded their assessment and warrant further study. Notwithstanding, non–present-on-admission diagnosis codes for CDI were relatively infrequent in both study groups (<2%) (Supplementary Table 9). The crude mortality rate in our study of 16.3% is lower than has been previously described [4, 6, 8]. However, our study also included a large proportion of non–critically ill patients, which likely contributed this difference. *Stenotrophomonas maltophilia* is a known colonizer of the respiratory tract, making discrimination between infection vs colonization difficult. This is true in our study, but also true in the real world for clinicians at the bedside. Our study highlights real-world use; thus, primary analysis was limited to patients actively treated for *S maltophilia* infection once the clinician made the decision to treat. If a cohort of patients was colonized and not infected with *S maltophilia*, this is likely nondifferential across both treatment groups. Additionally, this study demonstrates corroborative findings from mechanically ventilated patients, patients with vasopressor use, patients with SOFA score >2, and those with administrative indicators of hospital-onset pneumonia, which collectively mitigate this concern by enriching the data for likelihood of infection.

Our study suggests there is equipoise for an RCT comparing levofloxacin and TMP-SMX among hospitalized patients with *S maltophilia* infection. Sample size calculations extrapolated from our study findings (weighted mortality difference, 15.3% vs 19.1% between groups) suggest that 1548 patients per arm would be required to achieve an 80% power using a 2-sided $\alpha = .05$. However, protracted recruitment given relatively low incidence of *S maltophilia* and the potential lack of financial incentives for comparing 2 generic antibiotics represent potential hurdles.

CONCLUSIONS

Our large study of overlap-weighted cohorts of patients treated with levofloxacin vs TMP-SMX for *S maltophilia* LRTIs and

BSIs suggest that levofloxacin might be a reasonable alternative to the current accepted standard TMP-SMX for these infections. An RCT comparing levofloxacin and TMP-SMX head-to-head is yet to be performed. In the interim, large, rigorous observational studies may offer a valuable stopgap in evidence.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. S. S. K. conceived the study. S. H. S. and S. S. K. designed the study, conducted the literature search, and wrote the draft of the manuscript. S. H. S., S. W., and S. S. K. collected and analyzed the data. S. H. S., S. W., S. S. K., R. M., and V. G. F. interpreted the data. All authors reviewed and critically revised the manuscript for important intellectual content. The corresponding author had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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