Trimethoprim-Sulfamethoxazole *versus* Levofloxacin for *Stenotrophomonas maltophilia* Infections: A Retrospective Comparative Effectiveness Study of Electronic Health Records from 154 U.S. Hospitals

Sadia H. Sarzynski, Sarah Warner, Junfeng Sun, Roland Matsouaka, John P. Dekker, Ahmed Babiker, Willy Li, Yi Ling Lai, Robert L. Danner, Vance G. Fowler, Jr., Sameer S Kadri

SUPPLEMENTARY APPENDIX

Supplemental Methods

a. Sample Size Calculation

A prespecified sample size of n=500 patients per treatment was expected to allow for 80% power to detect a mortality rate difference 20% vs 28%, using 0.05-level 2-sided test. This was adjudicated by the authors as a clinically relevant difference in mortality.

b. Polymicrobial Infections

Polymicrobial infections were defined as those encounters that had additional cultures sampled from the same site on the same date that grew an organism other than *S. maltophilia.* To rule out falsely identifying polymicrobial infections due to preliminary microbiology results, reports identifying gram-negative bacillus and gram-negative rods were not considered.

Appendix Table 1: Antimicrobial Agents with Known Activity Against *Stenotrophomonas maltophilia*

A list of agents with known activity against *Stenotrophomonas maltophilia* in the literature was reviewed and applied as an exclusion criterion for case selection. This was done to enhance attribution of outcome to individual study drugs.

Antimicrobial Class	Antimicrobial Agent
Macrolide	Erythromycin
Tetracycline	Doxycycline, eravacycline, minocycline
Glycylcycline	Tigecycline
Fluoroquinolones	Moxifloxacin, ciprofloxacin
Polymyxin	Colistin
	Chloramphenicol
Beta-Lactams	Ticarcillin-clavulanate, ceftazidime, cefiderocol, cefepime

Other potentially active agents: Ceftazidime-avibactam, polymyxin B and omadacycline were not found to be used in the cohort of interest.

Appendix Table 2: Imputation of Missing Susceptibility Data

Approximately 10% of patients in the analysis cohort had no susceptibility data reported for the targeted therapy of interest in this study and were imputed to be susceptible to the therapy received. Patients who had susceptibility data for the culture and therapy of interest were only included if they were susceptible to the targeted therapy received.

Targeted Therapy	Susceptibility Available	Susceptibility Imputed
Levofloxacin	734 (89.2%)	89 (10.8%)
Trimethoprim-sulfamethoxazole	683 (90.1%)	75 (9.9%)

Appendix Table 3: Targeted Therapy by Infection Site

Targeted Therapy	Blood Culture	Respiratory Culture
Levofloxacin	99 (12.0%)	724 (88.0%)
Trimethoprim-sulfamethoxazole	64 (8.4%)	694 (91.6%)

Appendix Table 4: Conditions Defined by International Classification of Diseases (ICD) Codes

The study period spans through the transition of ICD-9-CM to ICD-10-CM.

	ICD Code(s)
Mechanical Ventilation	ICD9: 96.7, 96.71, 96.72 ICD10: 5A1935Z, 5A1945Z, 5A1955Z CPT: 94002, 94003
Cystic Fibrosis	ICD9: 277.00, 277.01, 277.02, 277.03, 277.09 ICD10: E84
Pneumonia	ICD9: 481, 485, 486, 514 ICD10: J18.0, J18.1, J18.2, J18.8, J18.9
Immunocompromised	ICD9: 279x, 266.2, 273.0, 273.1, 273.2, 277.2, 277.6, 288.1, 289.89 ICD10: D71x, D80x, D81x, D82x, D83x, D84x, D89x

Appendix Table 5: Imputation of Missing SOFA

SOFA on day of culture collection was included. The SOFA score was imputed missing as 0, under the assumption that the lack of laboratory tests or indicators of organ support on a given day (required to calculate a SOFA score) indicated a low clinical suspicion for abnormal results. The overall number of SOFA scores imputed as 0 were 58 of 1581encounters or 3.6%.

Targeted Therapy	SOFA Available	SOFA Imputed as 0
Levofloxacin	798 (97.0%)	25 (3.0%)
Trimethoprim-sulfamethoxazole	725 (95.6%)	33 (4.4%)

Appendix Table 6: Polymicrobial Culture by Organism

This table depicts polymicrobial culture by speciated organism if present with a frequency greater than 5 occurrences to allow the reader to view the most common organisms that were identified in polymicrobial cultures.

	Levofloxacin N=343		**Trimethoprim-sulfamethoxazole N=315**	
Organism	**Respiratory N=306**	**Blood N=37**	**Respiratory N=287**	**Blood N=28**
Speciated and Frequency of Occurrence ≥ 5	**N=224**	**N=21**	**N=193**	**N=9**
Acinetobacter baumannii	8	1	8	1
Citrobacter freundii	6	1	1	
Coliforms	5		7	
Enterobacter cloacae	20	2	15	2
Escherichia coli	9	1	7	2
Haemophilus influenzae	8		3	
Klebsiella oxytoca	7		8	2
Klebsiella pneumoniae	19	4	16	
Pseudomonas aeruginosa	52	5	39	
Serratia marcescens	16	1	17	
Staphylococcus aureus	51	5	60	2
Staphylococcus sp., Coag Positive	4		1	
Streptococcus pneumoniae	11		5	
Streptococcus sp., viridans group	5	1	5	

Appendix Table 7: Polymicrobial Infection by Culture Site

Targeted Therapy	**Infection Site**	**Polymicrobial Culture**	**Polymicrobial Culture Receiving Medication**
Levofloxacin	Blood	37 (37.4%)	21 (21.2%)
	Respiratory	306 (42.3%)	144 (19.9%)
Trimethoprim-sulfamethoxazole	Blood	28 (43.8%)	20 (31.2%)
	Respiratory	287 (41.4%)	158 (22.8%)

Appendix Table 8: Mechanical Ventilation Use in Overall Study Population

	Levofloxacin (n=823) N (%)	Trimethoprim sulfamethoxazole (n=758) N (%)
Any Mechanical Ventilation	257 (31.2%)	293 (38.7%)
Mechanical Ventilation in Window*	87 (10.6%)	78 (10.3%)

* Window restricts mechanical ventilation variable to +/- 3 days of culture drawn to determine severity of illness at time of infection.

Appendix Table 9: Frequency of non-Present on Admission (POA) coding for *Clostridioides Difficile* Infection

This diagnosis code is without temporality to targeted therapy treatment window and does not reflect the presence of symptoms, including diarrhea, or laboratory testing for *C. difficile*. Thus, it may or may not reflect clinical *C. difficile* infection diagnosed during the hospitalization.

Targeted Therapy	N (%) Non-POA *C. difficile* diagnosis code
Levofloxacin	9 (1.1%)
Trimethoprim-sulfamethoxazole	12 (1.6%)