Evaluation of the Treatment of *Stenotrophomonas maltophilia* in Tracheostomy-Dependent Pediatric Patients

Emma M. Tillman, PharmD, PhD; Sarah E. Firmani, PharmD; Veda L. Ackerman, MD; James E. Slaven, MS; and A. Ioana Cristea, MD, MS

OBJECTIVE Tracheostomy-dependent pediatric patients will often have respiratory cultures positive for *Stenotrophomonas maltophilia* (multidrug-resistant Gram-negative rod). There are limited data available to guide treatment in this population. The objective of this single-center, retrospective study was to evaluate if antibiotic treatment of *S maltophilia* improved clinical outcomes in tracheostomy-dependent pediatric patients.

METHODS We included tracheostomy-dependent pediatric patients who had a respiratory culture positive for *S maltophilia*. Patients were divided into 2 groups: 1) treatment and 2) no treatment.

RESULTS Forty patients with 55 encounters were included in this study. *S maltophilia* was treated with sulfamethoxazole-trimethoprim in 20 encounters (19 patients) and no antimicrobial treatment was given in 35 encounters (30 patients). The time to return to stable respiratory status was 5 days (0–10) (median [range]) in the treated group and 4 days (0–19) in the untreated group ($p = 0.52$). There was no statistically significant difference in time to baseline respiratory status between patients treated and those not treated for *S maltophilia*. There was no difference in hospital length of stay between patients who were or not treated.

CONCLUSIONS Based on these results, these data would suggest that there might not be a benefit to treating cultures positive for *S maltophilia* in tracheostomy-dependent pediatric patients.

ABBREVIATION SMX-TMP, sulfamethoxazole-trimethoprim

KEYWORDS child; gram-negative bacterial infections; lung diseases; *Stenotrophomonas maltophilia*; tracheostomy

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Introduction

Advances in neonatal and pediatric intensive care have reduced mortality but have introduced a new morbidity: a growing number of children who are medically stable but require chronic ventilatory support via tracheostomy at home.^{1,2} Tracheostomy-dependent pediatric patients with chronic respiratory failure are prone to chronic respiratory infections and in turn will often be treated with broad spectrum antibiotics.³ Antibiotic treatment can breed resistant bacteria and also can promote colonization of multidrug resistant bacteria.⁴ One of these multidrug resistant organisms found in cultures of children with chronic respiratory failure is *Stenotrophomonas maltophilia* (multidrug-resistant Gram-negative rod).⁵ At the time of obtaining culture results, it is often not known if this organism is a non-pathogenic colonization or the cause of a respiratory tract infection; this is especially true when patients may have other potential causes for increased respiratory distress such as a virus. In previous studies, prior use of oral quinolone and antipseudomonal antibiotics were associated with *S maltophilia*.⁶ Treat-

ing a colonization could increase a patient's risk for a more virulent and/or resistant infection. Additionally, *S maltophilia* is typically only susceptible to a few antibiotics including, trimethoprim-sulfamethoxazole, levofloxacin, ticarcillin-clavulanate, and doxycycline.^{7,8} There are limited data available to guide treatment of *S maltophilia* in this population of pediatric patients with chronic respiratory failure, and we are compelled to extrapolate evidence from either pediatric patients with cystic fibrosis or adult patients with chronic respiratory failure. The objective of this single-center, retrospective study was to evaluate if treating *S maltophilia* improved clinical outcomes in tracheostomy-dependent pediatric patients.

Materials and Methods

The institutional review board approved this retrospective study evaluating the utility of treating *S maltophilia* in tracheostomy-dependent pediatric patients with chronic respiratory failure. Patients were included in this study if they were admitted to the hospital with acute on chronic respiratory failure, received an infec-

tious work-up with respiratory, $\pm$ blood cultures, and had a respiratory culture positive for *S maltophilia* between August 2014 and March 2017. Patients were excluded if they had a history of cystic fibrosis or an allergy to sulfamethoxazole-trimethoprim (SMX-TMP). Our primary endpoint was time to return to baseline respiratory status, with a secondary endpoint of hospital length of stay. Data collection included demographic data, etiology of respiratory failure, need of mechanical ventilation at home, respiratory culture results, treatment regimen (drug, dose, and duration), number of days until return to baseline respiratory or ventilator settings, and length of hospital stay. Baseline respiratory status (tracheostomy collar or home ventilator setting) was defined as the settings described for each patient at the last outpatient visit, prior to the index admission with a culture positive for *S maltophilia* and included the following: baseline supplemental oxygen requirement, as well as baseline home ventilator settings. For patients who had positive cultures in the middle of a hospital admission, baseline respiratory status was defined as the settings for each patient 1 day prior to the acute illness that prompted respiratory cultures (surveillance respiratory cultures are not performed at our institution).

Respiratory secretions were obtained by blind bronchoalveolar lavage, which is standard of care at our institution. Blind bronchoalveolar lavage were obtained by using a lavage catheter (Combicath, KOL Biomedical Instruments, Chantilly, VA) that is introduced into the artificial airway through a bronchoscopy adapter on ventilator circuit (if patient is mechanically ventilated) or manual resuscitator. The catheter is advanced into the airway until gentle resistance is met, indicating that the catheter is “wedged” into a distal airway; 0.5 mL/kg of 0.9% NaCl is instilled through the catheter and then aspirated into the same syringe. The sample aspirate is then processed by the microbiology laboratory. At the time of cultures, all patients included in this study were initiated on at least a 48-hour infectious rule-out with broad-spectrum antibiotics (third or fourth generation cephalosporin and vancomycin), but not covering *S maltophilia*.

Patients were divided into 2 groups: 1) treatment and 2) no treatment. Each admission with a positive culture was considered a new encounter, so therefore some patients had multiple encounters. Two positive cultures were required to be separated by at least 14 days to be counted as an independent encounter. Additionally, some patients with long initial admission had multiple encounters within that single admission if these positive cultures were separated by at least 14 days. Statistical analysis was performed using Student *t* tests, with results being presented as means (SDs). Due to some variables being non-linear, and the inability of transformations to fix, Wilcoxon rank sum non-parametric methods were used in those cases, with results presented as medians (ranges). Categorical

Table 1. Patients With Multiple Encounters

Patient	Treatment	Time From Previous Positive Cultures (days)
Patient 1		
Encounter 1	No	
Encounter 2	Yes	17
Patient 2		
Encounter 1	No	
Encounter 2	Yes	239
Patient 3		
Encounter 1	No	
Encounter 2	Yes	20
Patient 4		
Encounter 1	No	
Encounter 2	Yes	142
Patient 5		
Encounter 1	Yes	
Encounter 2	No	511
Patient 6		
Encounter 1	Yes	
Encounter 2	No	507
Encounter 3	No	98
Patient 7		
Encounter 1	No	
Encounter 2	Yes	173
Patient 8		
Encounter 1	Yes	
Encounter 2	No	260
Patient 9		
Encounter 1	No	
Encounter 2	No	37
Encounter 3	No	179

variable comparisons were performed using χ^2 tests, with Fisher exact tests being used to verify when cell counts were small. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Between August 2014 and March 2017, we identified 43 tracheostomy-dependent patients who had positive cultures for *S maltophilia*. Of those, 2 were excluded—1 for an allergy to SMX-TMP and 1 due to underlying cystic fibrosis diagnosis. Forty patients with 55 unique encounters were included in this study. *S maltophilia* was treated with a median dose of SMX-

Table 2. Demographic Data

	Treated (19 Patients, 20 Encounters)	Not Treated (32 Patients, 35 Encounters)	p value
Male, n (%)	11 (55)	24 (69)	0.31
Female, n (%)	9 (45)	11 (31)	
Age (yr), mean $\pm$ SD	3.24 $\pm$ 5.99	1.90 $\pm$ 3.02	0.36
Ethnicity			1.00
White, n (%)	16 (80)	26 (74)	
Asian, n (%)	0 (0)	1 (3)	
Black, n (%)	4 (20)	8 (23)	
Indication for tracheotomy and/or mechanical ventilation			0.66
Chronic lung disease of prematurity, n (%)	12 (63)	24 (75)	
Musculoskeletal/anatomical airway abnormality, n (%)	2 (11)	2 (6)	
Neurological, n (%)	5 (26)	6 (19)	

TMP 11.6 mg/kg/day (range, 5.2–20.6) (based on TMP) in 20 encounters (19 patients), and no antimicrobial treatment was given in 35 encounters (30 patients). There were nine patients included in this study that had multiple encounters (Table 1). There was no difference in age, sex, or ethnicity between the 2 groups (Table 2). Patients who were treated with SMX-TMP had significantly higher concentrations in colony forming units per milliliter of *S maltophilia* in respiratory cultures ($p < 0.01$) (Figure 1). There was not a significant difference in treatment based on the presence of other organisms in the respiratory cultures. The majority of patients had cultures positive for multiple organisms and not just *S*

maltophilia. The most common organisms identified were *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus*, *Serratia marcescens*, yeast, and methicillin-susceptible *Staphylococcus aureus*. A complete list of organisms can be found in (Table 3). Only 2 patients in the treated group did not have another organism identified in the respiratory cultures and 4 patients in the no treatment group did not have other organisms identified. Additionally, we evaluated if the presence of tracheostomy alone vs tracheostomy with mechanical ventilation affected treatment. Patients with a tracheostomy and mechanical ventilation were treated 36% of all en-

Figure 1. Concentration of *Stenotrophomonas maltophilia* in respiratory cultures ($p=0.45$).

Table 3. Microorganisms Identified Respiratory Cultures*

Microorganism	Treated for <i>Stenotrophomonas maltophilia</i>	Not Treated for <i>Stenotrophomonas maltophilia</i>
<i>Klebsiella pneumoniae</i>	7	8
<i>Pseudomonas aeruginosa</i>	8	6
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	6	8
<i>Serratia marcescens</i>	4	6
Yeast	4	3
Methicillin-susceptible <i>Staphylococcus aureus</i> (MSSA)	3	3
<i>Enterobacter cloacae</i>	2	4
<i>Streptococcus</i> sp.	2	3
<i>Achromobacter</i>	2	1
<i>Escherichia coli</i>	2	1
<i>Citrobacter freundii</i>	1	2
<i>Chryseobacterium</i>	1	2
<i>Proteus mirabilis</i>	1	1
<i>Alcaligenes faecalis</i>		1
Coagulase-negative staph		1
<i>Moraxella catarrhalis</i>		1
<i>Burkholderia pickettii</i>		1

* Numbers indicate numbers of patients with cultures positive for each organism. Several patients had respiratory cultures that were positive for multiple organisms.

counters compared with patients with a tracheostomy and no mechanical ventilation were treated 63% of all encounters, but due to the small sample of patients in the tracheostomy alone group, this result was not statistically significant (Figure 2).

The time to return to baseline respiratory status was 5 days (0–10) (median [range]) days in the treated group and 4 days (0–19) ($p = 0.87$) (Figure 3). The mean hospital length of stay was 9 days (0–374) and 7 days (1–274) (median [range]) in the treated and untreated groups, respectively ($p = 0.42$) (Figure 4).

Discussion

This is the first study to evaluate if the treatment of *S maltophilia* improved outcomes in tracheostomy-dependent pediatric patients with chronic respiratory failure. We found that, regardless of treatment, both groups had a return to baseline respiratory status in approximately 4 to 5 days. Our results are similar to the findings of a recent multicenter, retrospective cohort study revealing a median hospital length of stay of 4 days for acute bacterial tracheostomy-associated

Figure 2. Treatment of patients with *Stenotrophomonas maltophilia* infections categorized by presence or absence of mechanical ventilation.

Figure 3. Time to return to baseline respiratory settings ($p=0.87$).

respiratory tract infections.⁹ However, the overall hospital length of stay in our study was much longer than published in previous studies. This was because we included all inpatient tracheostomy-dependent patients who had positive cultures for *S maltophilia*, and these positive cultures may have occurred during the initial admission, when the caregivers received training for transition to home ventilation. Many of these patients have an initial inpatient admission of 4 to 9 months due to prematurity, tracheostomy placement, transition to a home ventilator, and parent and caregiver training safely to go home with their tracheostomy-dependent child.¹⁰

Because this was a retrospective study and the choice of when to treat and when not to treat was physician dependent based on the patient's physical examination and clinical findings, we evaluated the presence of other positive bacterial or viral cultures and the number of colony forming units of the *S maltophilia*. We can speculate that these variables may have influenced whether to treat or not to treat; for example, if a patient had an acute clinical decompensation and the only positive culture was for *S maltophilia*, then a clinician might be more inclined to treat the *S maltophilia* as compared with a patient who looked equally sick with a positive viral or other bacterial culture and a culture positive for *S maltophilia*. Additionally, all patients included in this study received at least a 48-hour infectious rule-out with broad-spectrum antibiotics, but not covering *S maltophilia*. If a patient's respiratory status had improved by the time the culture data were available and the *S maltophilia* had not been treated, a clinician may have been more likely to attribute the respiratory decline to a virus or another bacteria present in cultures opposed to *S maltophilia*. Interestingly,

our hypothesis was not validated by the data. Only 11% off all patient encounters had cultures that were only positive for *S maltophilia* without the presence of another organism. The concentration of *S maltophilia* in the respiratory culture did show to be a significant factor for a clinician choosing to treat the acute respiratory infection.

Although we are not aware of any studies evaluating the treatment of *S maltophilia* in tracheostomy-dependent pediatric patients, another group of pediatric patients who are prone to infections and/or colonization with *S maltophilia* are patients with cystic fibrosis, and there are data for guiding treatment of *S maltophilia* in this population. A Cochrane Review recently concluded that there is insufficient evidence for treating *S maltophilia* in patients with cystic fibrosis.⁴ Although this is a different patient population with unique lung pathology, this was a very large review of another group of patients who also have chronic respiratory colonization, and there has been a dilemma in whether to treat or not to treat.

Several investigators have evaluated the use of antibiotics in treatment of acute respiratory infections in tracheostomy-dependent pediatric patients. McCaleb et al¹¹ recently conducted a retrospective descriptive study to characterize bacteria grown in respiratory cultures of tracheostomy-dependent pediatric patients. These investigators reported culture data from 93 patients, and isolated *Pseudomonas aeruginosa* was identified in 90% of cultures and *S maltophilia* was identified in 77% of cultures.¹¹ They noted that specific organisms were not related to level of respiratory support or the likelihood of receiving antibiotics, yet they did not specifically address the incidence of treatment of cultures positive for *S maltophilia*.

Figure 4. Length of hospital stay ($p=0.42$)

In a 2012 study evaluating the utility of surveillance tracheal cultures in accurately predicting organisms responsible for acute respiratory infections in pediatric patients with tracheostomy tubes, the authors showed that there are significant changes in bacteria cultured and antibiotic sensitivity between consecutive tracheal cultures, and prior culture data have limited utility in choosing empiric antibiotics.¹²

In our study, we only evaluated the treatment of *S maltophilia* with SMX-TMP due to our clinical laboratory, which only reports susceptibilities for *S maltophilia* for 3 antibiotics: SMX-TMP, minocycline, and moxifloxacin. Because tetracyclines are known to cause tooth enamel hypoplasia, or permanent tooth discoloration, and fluoroquinolones are associated with a risk of tendinitis and tendon rupture, SMX-TMP is the first-line therapy for treating *S maltophilia* at our institution.

Although our study is the first in this patient population, it is not without limitations. Our study is limited in that it is a retrospective observational study with a relatively small sample size. We were limited only to data that were available in the electronic medical record; therefore, we may have missed clinical observations that influenced the clinician's decisions to treat or not to treat *S maltophilia* infections.

We identified no statistically significant difference in time to baseline respiratory status between patients treated and those not treated for *S maltophilia*. We identified no difference in hospital length between patients who were and were not treated. This study was retrospective and did not evaluate SMX-TMP dosing, but based on these results, these data would suggest that there might not be a benefit to treating cultures

positive for *S maltophilia* in tracheostomy-dependent pediatric patients with chronic respiratory failure.

ARTICLE INFORMATION

Affiliations Indiana University School of Medicine (EMT, VLA, JES, AIC), Indianapolis, IN; Riley Hospital for Children at Indiana University Health (EMT, SEF, VLA, AIC), Indianapolis, IN

Correspondence Emma M. Tillman, PharmD, PhD;
emillma@iu.edu

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