Nebulized Gentamicin as an Alternative to Nebulized Tobramycin for Tracheitis in Pediatric Patients

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OBJECTIVES Tracheitis is an infection of the lower respiratory tract and is defined by the US Centers for Disease Control and Prevention (CDC) based on signs and symptoms with no radiographic evidence of pneumonia. One method of treatment involves the use of tobramycin given by nebulizer. The purpose of this study was to compare the safety and efficacy of nebulized gentamicin with nebulized tobramycin.

METHODS This study was conducted in patients under 21 years of age who received greater than or equal to 1 day of gentamicin, 80 mg, or tobramycin, 300 mg, given twice a day by nebulization within the 14-month study period. The primary endpoint was amount of time until the patient no longer met the CDC definition of tracheitis.

RESULTS There were 19 patients who presented with 60 separate encounters. The average age of the patients within the gentamicin group was 7.2 and 5 years old within the tobramycin group. The average duration of time for the gentamicin treatment encounters to be free of the CDC definition of tracheitis was 3.36 days compared to 3.17 days with tobramycin. No adverse effects were observed that were attributable to aminoglycoside nebulization.

CONCLUSIONS No differences were detected between the safety and efficacy of intravenous gentamicin administered twice a day by nebulizer and that of tobramycin inhalation solution given twice daily in children without cystic fibrosis.

ABBREVIATIONS CDC, Centers for Disease Control and Prevention; CF, cystic fibrosis

KEYWORDS aerosolized antibiotics; aerosolized gentamicin; gentamicin; nebulized gentamicin; pediatrics; tobramycin; tracheitis

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Introduction

Tracheitis is defined as an infection of the upper respiratory tract. It typically presents with signs and symptoms of tachypnea, stridor, hoarseness, fever, cough, and an increase and/or discoloration of respiratory secretions.¹ Patients who have a tracheostomy or who are on mechanical ventilation are at higher risk for tracheitis due to the patient's dependence on technology that bypasses the native protection of the upper tract (nose, mouth, and upper airway).¹⁻³ The endotracheal tubes used in ventilation may serve as a portal for various bacteria to enter the respiratory tract and subsequently colonize, potentiating the risk for infection.^{4,5}

The US Centers for Disease Control and Prevention (CDC) defines tracheitis based on the following criteria: positive culture obtained by deep tracheal aspirate or bronchoscopy and at least 2 signs or symptoms with no other recognizable causes (i.e., fever $>38^{\circ}\text{C}$, cough, new or increased sputum production, rhonchi, and wheezing). There also should be no evidence of pneumonia, given a chest radiograph. Diagnosis is simi-

lar for infants, with additional symptoms of respiratory distress, apnea, and bradycardia also being indicative of tracheitis.⁶

Patients in whom tracheitis is diagnosed commonly grow *Staphylococcus aureus*. In ventilated patients, *Pseudomonas aeruginosa* is also a common cause of both upper and lower respiratory tract infections.^{2,7} Common microorganisms in patients with tracheostomy requiring long-term ventilation include *Haemophilus influenza*, *Acinetobacter baumannii*, and *Serratia* spp in pediatric and adult patients.^{8,9}

There are currently no clinical guidelines for the treatment for tracheitis. For the treatment and prevention of tracheitis in the non-cystic fibrosis (CF) pediatric population, tobramycin solution for inhalation is often used despite its lack of approval by the US Food and Drug Administration for this indication. The use of nebulized aminoglycoside therapy in patients with CF is an established practice that has been proven to be a safe and effective therapy. This has been thoroughly reviewed and assessed by the Cystic Fibrosis Foundation, a European consensus committee, and a Cochrane review.¹⁰⁻¹² Less is known about the safety

Table 1. Patient Findings

	Gentamicin	Tobramycin
Number of patients	14	12
Number of patient encounters	30 (50%)	30 (50%)
Patient encounters with AG prophylaxis	14 (58%)	10 (42%)
Patient Encounters with AG Treatment	15 (45%)	18 (55%)
Patient encounters with AG empiric treatment*	1 (33%)	2 (67%)

AG, aminoglycoside

*Empiric treatment is defined as encounters in which antibiotic treatment is initiated prior to drawing a sputum culture

and efficacy profiles of these nebulized medications in patients without CF, which warrant further studies.¹³ Nonetheless, there are benefits in choosing nebulized antibiotic therapy for treating infections confined to the respiratory tract. The most important benefit is the ability to deliver bactericidal doses of antibiotic directly to the site of infection rather than by the systemic route, which could predispose patients to unnecessary adverse effects as well as avoid the need for invasive intravenous access. Aminoglycosides achieve bactericidal activity by a concentration-dependent means of killing, thus, the delivery of the drug directly to the site of infection is ideal.¹⁴

The purpose of this study was to compare the safety and efficacy of nebulized gentamicin with that of tobramycin. Similar to tobramycin, gentamicin is an aminoglycoside antibiotic with the same bactericidal mechanism of action and a comparable spectrum of activity encompassing Gram-negative and -positive pathogens. The use of gentamicin may provide a therapeutic and more cost-effective alternative for treating tracheitis in children.

Materials and Methods

The study took place at Ranken Jordan Pediatric Bridge Hospital, a 34-bed inpatient pediatric rehabilitation hospital located in Maryland Heights, Missouri. The patients cared for at the institution are those who are frequently dependent on tracheostomy and ventilation, who warrant extra medical care to provide them with a bridge from acute care hospital to home. Study oversight was conducted by the institution as well as the Southern Illinois University of Edwardsville Institutional Review Board, which waived the requirement for individual informed consent.

The study consisted of retrospective data from pediatric patients with tracheostomy tubes admitted to the hospital, who received greater than or equal to 1 day of therapy with either nebulized injectable gentamicin, 80 mg twice daily, or tobramycin inhalation solution, 300 mg twice daily, between August 2012 and October 2013 (14 months). The 10 mg/mL sterile, nonpyrogenic, preservative-free gentamicin solution and the tobramycin solution used in this study were given through the tracheostomy site using a jet nebulizer. Patient eligibility

required that subjects meet limited criteria: patients had to be under 21 years of age, without CF, and had received routine prophylaxis or treatment of tracheitis at the hospital during the study period. Additionally, the subjects being treated for tracheitis must have met the CDC definition of tracheitis as discussed above. Patients were excluded who received doses other than 300 mg of tobramycin or 80 mg of gentamicin.

To establish whether gentamicin is comparable to tobramycin, analysis involved days of elevated temperature, days of increased respiratory treatment (e.g., short-acting beta agonist and/or oral steroid burst), days of supplemental oxygen above baseline, days of symptoms until resolution, days of abnormal tracheal secretion (e.g., amount, color, viscosity), and whether the patient warranted a transfer to an acute care facility. Patient encounters were included rather than individual patients to allow for patients to serve as their own controls for recurring bouts of tracheitis during this 14-month period. The endpoints of this study were aggregated and analyzed to determine the duration of time that the patient encounters no longer met the CDC definition of tracheitis as discussed previously. This measurement was compared by using a 2-sample Student *t*-test. Patient demographics were also compared using a 2-sample Student *t*-test for continuous data and Fisher's exact test for nominal data. Unless otherwise noted, data are mean $\pm$ SD.

Results

Sixty patient encounters met the study's inclusion parameters; 30 encounters of gentamicin and 30 encounters of tobramycin (Table 1). Patient demographics appear to have been evenly distributed (Table 2). The breakdown of the pathogenic organisms was evenly distributed for the gentamicin and tobramycin encounters (Table 3). The organism isolated most frequently in tracheal aspirates was *P aeruginosa*, followed by *Serratia marcescens*. The minimum inhibitory concentrations (MIC) for the nebulized gentamicin and tobramycin groups were uniform for the most common organism, *P aeruginosa*.

The mean duration of treatment for gentamicin was 12.82 ± 4.62 (range 7-22) days, and the mean duration of tobramycin treatment was 10.5 ± 1.89 (range 8-14)

Table 2. Patient Demographics Stratified by Aminoglycoside

	Gentamicin (n = 14)	Tobramycin (n = 12)	p Value
Females	7 (50%)	6 (50%)	1
Age, yr	7.24 ± 7.08	5.04 ± 5.54	0.39
Weight, kg	22.74 ± 15.94	19.56 ± 13.22	0.59
Respiratory disease			
Lung disease*	8 (57%)	5 (42%)	0.7
CNS dysfunction†	7 (50%)	4 (33%)	0.45
Genetic mutation‡	2 (14%)	3 (25%)	0.63

CNS, central nervous system

* Lung diseases include bronchopulmonary dysplasia or chronic lung disease secondary to prematurity of birth, tracheomalacia, bronchomalacia, and laryngomalacia

† CNS dysfunction includes cerebral palsy, spina bifida, lissencephaly, hypoxic-anoxic brain injury, and respiratory dystonia

‡ Genetic mutations include Hunter syndrome, Marfan syndrome, dystonia (DYT6), and trisomy 21

days, excluding the patients who had to transfer to an outside institution due to a worsening in respiratory symptoms. The mean duration of time required for encounters within the gentamicin group to no longer meet the CDC definition of tracheitis was 3.36 ± 1.57 (range 2-7) days. This was compared to 3.17 ± 1.64 (range 2-7) days required for encounters within the tobramycin group to no longer meet the CDC definition (Table 4). The amount of time until this definition was no longer met was not significantly different between the gentamicin and tobramycin encounters ($p = 0.77$). If multiple encounters for an individual patient were aggregated and represented as an average value per patient, the amount of time to no longer meet the CDC definition of tracheitis was 3.21 and 3.09 days for gentamicin and tobramycin patients, respectively. The time until reinfection was also reviewed for both the gentamicin and tobramycin groups. The average lengths of time until tracheitis reinfection in these patients were similar: 47 days in the gentamicin group and 39 days within the tobramycin group.

No adverse effects were observed that were attributable to either gentamicin or tobramycin nebulization. Perceived side effects that could have occurred included cough, airway irritation, and bronchoconstriction, among others. All patients during and after the aminoglycoside nebulization did not have any documentation of additional or worsening of existing respiratory symptoms. In addition, there was no documentation regarding patient encounters within the study exhibiting worsening degree of nephrotoxicity or ototoxicity above baseline. There were 3 patient encounters which warranted a transfer to an outside acute care hospital due to deterioration of respiratory status. Two of these patients were in the gentamicin treatment group, and 1 of the patients was from the tobramycin treatment group. Of these 3, 1 of the patients was found to have a viral tracheitis while the others had polymicrobial tracheitis.

Discussion

Within this study, we did not observe a difference between the amount of time required for nebulized gentamicin patients to no longer meet the CDC definition of tracheitis and the time required for the nebulized tobramycin patients. The distinctions between the 2 medications were not observed using the aggregate endpoints of days of signs and symptoms, days of increased temperature, days of supplemental O₂ above baseline, days of abnormal tracheal secretions, and rescue medication use. As these were 2 small sample sizes, even though we did not observe a difference between our patient populations, we cannot deny the potential existence of type II error which would have resulted in a lack of power to detect a difference between the groups.

The studies that define the optimal treatment of bacterial tracheitis within the pediatric population are limited.¹⁵ In addition, the optimal treatment duration with nebulized antibiotics also remains unclear. For the treatment with systemic therapies, studies recommend 10- to 14-day treatment courses.¹⁶ The patients in our study resolved the CDC definition of tracheitis after approximately 3 days with nebulized therapy in both groups, despite the patients receiving treatment for an average of 10.5 and 12.82 days (tobramycin and gentamicin groups, respectively). This poses the question of whether this duration of treatment with nebulized therapy may be excessive in these patients. In a study by Tamma et al,¹⁷ 150 pediatric patients received systemic antibiotics for ventilator-associated tracheitis with the primary endpoint of determining whether prolonged courses (≥ 7 days) were superior to shorter course (< 7 days). What the authors found was that prolonged courses not only provided no statistical difference in outcomes compared to the shorter durations of therapy, but they also were associated with significantly increased risk of acquiring multidrug-resistant organisms.

Table 3. Organism Isolates

Organism	Gentamicin	Tobramycin	p Value
<i>Pseudomonas aeruginosa</i>	12 (40%)	14 (45.2%)	0.8
<i>Serratia marcescens</i>	9 (30%)	7 (22.6%)	0.57
<i>Escherichia coli</i>	1 (3.3%)	2 (6.5%)	1
<i>Acinetobacter baumannii</i>	2 (6.7%)	1 (3.2%)	0.61
<i>Achromobacter xylosoxidans</i>	1 (3.3%)	2 (6.5%)	1
<i>Staphylococcus aureus</i> (MRSA)	0 (0%)	3 (9.7%)	0.24
<i>Staphylococcus aureus</i> (MSSA)	0 (0%)	2 (6.5%)	0.49
<i>Streptococcus pneumoniae</i>	2 (6.7%)	0 (0%)	0.24
<i>Moraxella catarrhalis</i>	1 (3.3%)	0 (0%)	0.49
<i>Enterobacter cloacae</i>	1 (3.3%)	0 (0%)	0.49
<i>Alcaligenes faecalis</i>	1 (3.3%)	0 (0%)	0.49
MIC for <i>Pseudomonas aeruginosa</i>			
Resistant (MIC > 8)	8 (67%)	9 (64%)	1
Intermediate (MIC = 8)	2 (17%)	2 (14%)	1
Sensitive (MIC ≤ 4)	2 (17%)	3 (21%)	1

MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *S aureus*; MSSA, methicillin-sensitive *S aureus*

The safety profiles of nebulized antimicrobials used in the treatment of tracheitis have not been thoroughly reported, with the exception of tobramycin.¹⁸ In this study, there were no reported adverse effects that occurred during or immediately after gentamicin or tobramycin nebulization. Although adverse effects of nebulized antimicrobial agents are often respiratory issues, they may have been masked by the patient's acute respiratory illness.¹⁸

The gentamicin used within this study was manufactured for injectable use which may not be optimal for nebulized administration. The physical properties of intravenous products have been reported to contribute to local adverse effects such as cough, airway irritation, and bronchoconstriction.¹⁸ In terms of acidity, the pH of gentamicin falls within the acceptable range for inhaled products. The particular gentamicin solution we used had a pH ranging from 3 to 5.5, whereas the acceptable range for inhaled products is 2.6 to 10, making it appropriate for nebulized therapy.¹⁸⁻²⁰ The osmolality from nebulized antibiotic therapy, which could result in adverse effects, is <100 or >1100 mOsm/L.²⁰ In our study, the osmolality for the gentamicin solution used and was measured at 39 mOsm/L. This value was achieved through the average of 5 readings from a vapor pressure osmometer. Although a hypo-osmolar solution was used, there were no reports of adverse effects secondary to the administration of gentamicin. The osmolality of tobramycin was not assessed.

As with all antibiotics, there is always a concern for bacterial resistance against our available arsenal of antibiotics, and aminoglycosides are no exception. The degree or potential for resistance was not analyzed

within the study. However, one of the chief benefits of using nebulized aminoglycoside therapy is that a high concentration of drug is delivered directly to the site of infection. In a study by Twiss et al,²⁰ pediatric patients had sputum concentration drawn after receiving nebulization with 80 mg of gentamicin. The mean sputum concentration was 624 mg/g, which greatly exceeded the MIC of the predominant respiratory pathogens 25-fold. Typical references suggest the peak aminoglycoside concentration to MIC ratio of 4:1 is optimal to ensure bactericidal killing with aminoglycosides. Higher drug concentrations appear to correlate with better patient outcomes given the concentration-dependent profile of aminoglycosides.²¹

The use of gentamicin was significantly more cost effective than tobramycin in the study and is a motivating factor toward seeking alternative therapies. At the study onset, intravenous gentamicin was nearly 8-fold less expensive than the tobramycin product using the study center's acquisition costs. As brand name tobramycin recently lost its market exclusivity in 2013, less expensive generic agents are available but are still significantly more expensive than intravenous gentamicin.

A notable difference within the gentamicin and tobramycin groups was the difference in use of rescue medications (54.5% and 83.3%, respectively). A potential rationale for this is due to the retrospective, unblinded nature of the study. As the medical staff has more experience with tobramycin nebulized therapy, there may have been a tendency to select the sicker patients to receive this therapy. Additionally, the patients in the tobramycin group had more fevers than those in the gentamicin group. Upon examining the data

Table 4. Efficacy Analysis

	Gentamicin	Tobramycin	p Value
Mean no. of days of signs and/or symptoms*	2.82 [†]	2.75	0.95
Mean no. of days of increased temperature	0.09	0.92	0.01
Mean no. of days of use of supplemental O ₂ above baseline	2.18	2.75	0.67
Mean no. of days of abnormal tracheal secretions	3.45	2.92	0.59
% Encounters using rescue medication [‡]	54.5%	83.3%	0.19
Encounters warranting transfer to an outside institution	2 encounters	1 encounter	1
Mean no. of days until CDC definition are no longer met	3.36	3.17	0.77

CDC, US Centers for Disease Control and Prevention

* Signs and/or symptoms include fever, cough, abnormal sputum, rhonchi, wheeze, symptoms of respiratory distress, apnea, bradycardia, tachycardia, tachypnea, increased work of breathing, elevated end-tidal CO₂, shallow breaths, and persistent cough

[†] Excluding 1 encounter with mildly elevated end tidal CO₂ that spanned the entire duration of treatment.

[‡] Rescue medication is defined as encounters requiring short-acting beta agonist and/or stress dose oral steroids to treat respiratory distress in patients with a history of bronchopulmonary dysplasia

and timeframe of patients, this does not appear to be the case, as patients from either group were selected within a 7-month timeframe each. Additionally, patients in the tobramycin group with a persistent low-grade fever might have inflated the group's average. This may be better explained by standard patient variability within a small study.

A limitation in this study was the inability to rule out pneumonia with the onset of symptoms indicative of a lower respiratory tract infection. As chest radiographs were not performed within the institution, this hampered our ability to rule pneumonia out of the differential diagnosis. Another disadvantage of the study was that the degree of systemic exposure of aminoglycosides was not assessed. In a committee report from the American Academy of Pediatrics Committee of Infectious Diseases, the authors outline the extent of systemic exposure for pediatric patients receiving nebulized gentamicin.²² The report cites studies which gave varying doses of nebulized gentamicin in various concentrations (120-, 360-, and 600-mg) as a single dose to pediatric patients. The highest peak plasma concentration from the 600-mg dose was 4.2 mg/L (mean 2.48 mg/L) and was undetectable after 8 hours. This study demonstrated that systemic absorption of nebulized therapy with gentamicin occurs in a dose-dependent fashion but also shows that with very large doses, only small amounts reach the systemic circulation. Drug accumulation was not demonstrated in this study.²³ Serum aminoglycoside levels may be considered if accumulation is suspected, particularly in patients with renal dysfunction or in patients taking nephrotoxic medications.

Conclusions

We were unable to detect a difference between the safety and efficacy of intravenous gentamicin administered twice a day by nebulizer and that of tobramycin

inhalation solution given twice daily in children without cystic fibrosis. The lack of well-designed studies of the efficacy and safety profiles of nebulized gentamicin in this patient population demonstrates the need for further research to be conducted. Additionally, the optimal treatment duration of nebulized aminoglycosides for the treatment of tracheitis has yet to be defined.

ARTICLE INFORMATION

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