JPPT | Survey Study

Inhaled Tobramycin Usage in Critically Ill Pediatric Patients Without Cystic Fibrosis: A Pediatric Pharmacy-Association, Practice-Based Research Network Survey Study

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OBJECTIVE The purpose of this study was to characterize reported usage, dosage regimens, and monitoring practices of inhaled tobramycin in health systems with neonatal intensive care units (NICUs), pediatric intensive care units (PICUs), and cardiovascular intensive care units (CICUs) from the members of the Pediatric Pharmacy Association (PPA). The primary objective was to identify the number of respondents who use an inhaled tobramycin protocol. The secondary objectives included the main indications, dosage regimens, monitoring parameters used, and administration details for inhaled tobramycin.

METHODS A cross-sectional questionnaire was distributed to PPA members from March 28–May 22, 2023. Descriptive statistics were employed.

RESULTS The questionnaire was completed by respondents at 79 institutions; respondents at 61 institutions used inhaled tobramycin in PICUs (n = 45; 73.8%), NICUs (n = 36; 59.0%), and CICUs (n = 14; 23.0%). Most respondents (n = 73; 92.4%) in the 61 institutions that use inhaled tobramycin did not have an established protocol. The most common tobramycin product used was a tobramycin nebulization solution, and the most common indication was ventilator-associated tracheitis. Respondents noted the most common dosage regimen was 40 to 80 mg every 8 to 12 hours or 150 mg every 12 hours, regardless of patient age. Most respondents were unaware of the nebulizer used and the location of the nebulizer within the ventilator circuit. Additionally, the respondents noted that their intensive care units do not routinely check tobramycin serum concentrations.

CONCLUSION Most respondents did not have a standardized inhaled tobramycin protocol. There are variations in the dosage regimen, administration, and monitoring practices in critically ill children receiving inhaled tobramycin. Pediatric clinical pharmacists should work with interprofessional teams, including respiratory therapists and providers, to standardize the use of inhaled antibiotics.

ABBREVIATIONS AKI, acute kidney injury; CF, cystic fibrosis; CICU, cardiac intensive care unit; ICU, intensive care unit; IDSA: Infectious Diseases Society of America; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit; PBRN, Pharmacy Practice-Based Research Network; PPA, Pediatric Pharmacy Association; VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheitis

KEYWORDS pediatrics; inhaled tobramycin; acute kidney injury; mechanical ventilator; pharmacokinetics; nebulizers

J Pediatr Pharmacol Ther 2025;30(3):332–339

DOI: 10.5863/JPPT-24-00061

Introduction

In critically ill children with respiratory infections, such as ventilator-associated pneumonia (VAP) or ventilator-associated tracheitis (VAT), inhaled antibiotics are a potential treatment option. The 2016 Infectious Diseases Society of America (IDSA) guidelines for adults with VAP and hospital-acquired pneumonia recommend using inhaled colistin or aminoglycosides in addition to systemic antibiotics for patients with multidrug-resistant organisms.[1] However, there are no consensus recommendations on the use of inhaled antibiotics in critically ill children for VAP or VAT. In addition, there is a paucity of data on the efficacy and safety of inhaled antibiotics in critically ill adults and children.[2]

Several case reports and studies have evaluated the use of inhaled tobramycin in critically ill adults and

children.[3–11] Most of the case reports have described reports of critically ill patients with detectable tobramycin troughs and acute kidney injury (AKI).[3–6] Geller and colleagues[12] conducted a pharmacokinetic study in 258 patients with cystic fibrosis (CF) in the ambulatory care setting receiving inhaled tobramycin 300 mg twice daily by a PARI LC PLUS (Pari Respiratory, Midlothian, VA) nebulizer. They found that patients had a mean peak concentration of 1.2 mcg/mL, 1 hour after dosing and undetectable trough concentrations. However, 5 studies have evaluated the incidence of detectable serum concentrations in adults and children, with the majority being critically ill and without CF; these investigators found between 8.3% and 68.2% of patients had detectable serum concentrations, and up to 24.3% of patients developed AKI.[7–11] Several studies identified risk factors for detectable tobramycin serum concentrations, including mechanical ventilation, increased age, and AKI or chronic kidney disease at the time of inhaled tobramycin initiation.[9–11] However, the results of these studies are limited in that different tobramycin products, dosage regimens, nebulizer devices, and mechanical ventilator set-ups were used between studies.

There are many unknowns regarding inhaled tobramycin use in critically ill children regarding dosage regimen, type of nebulizers used, and placement of the nebulizer within the ventilator system. These factors are crucial as they potentially contribute to the variability in patient outcomes, such as detectable serum drug concentrations and the incidence of AKI. The purpose of this study was to characterize reported usage, dosage regimens, and monitoring practices of inhaled tobramycin in health systems with neonatal intensive care units (NICUs), pediatric intensive care units (PICUs), and pediatric cardiovascular intensive care units (CICUs). By identifying inconsistencies in current practices, this research aims to gather essential data that could support the development of standardized protocols, ultimately enhancing the safety and efficacy of inhaled tobramycin treatments in this vulnerable population.

Materials and Methods

Study Design and Survey Administration. This was a descriptive survey study of pediatric clinical pharmacists. The survey included 74 questions, including health-system demographics, policies of inhaled antibiotics for non-CF patients in the NICU, PICU, and CICU, inhaled tobramycin administration details, tobramycin product and dosage regimen, and monitoring considerations. Questions were asked separately for each unit type, consisting of multiple choice, mark all that apply, and text entry. Although the questionnaire included 74 questions, the length depended upon the number of units chosen. A summary of these questions is found in the Supplemental Appendix.

The electronic questionnaire was developed and distributed through Qualtrics (Provo, Utah) and sent through email using the Pediatric Pharmacy Association's (PPA) Pharmacy Practice-Based Research Network (PBRN) from March 28–May 22, 2023, with 2 reminder emails sent during the time frame. PPA members could forward the questionnaire link to nonmembers at their institution for increased participation. Based on the information provided by the PPA Interim Executive Director, the questionnaire was sent to approximately 957 pharmacist members representing 310 health systems, which included 268 NICUs (86.5%), 178 PICUs (57.4%), and 70 CICUs (22.6%). Clinicians were asked to provide the first 2 letters of the hospital street and the last 3 digits of the hospital zip code to ensure that duplicate responses did not occur. Participation in the survey was voluntary and anonymous. Incomplete surveys were excluded from the analysis.

Study Objectives and Data Analysis. Demographic data collected included geographical location (i.e., Northeast, Midwest, Southeast, Southwest, West) of the institution, number of pediatric beds, which intensive care unit(s) (ICU) in the institution used inhaled tobramycin in patients without CF, and whether the unit has a protocol for the use of inhaled antibiotics in critically ill patients without CF. Regarding each unit, the number of beds, along with components of the protocol (if applicable), were collected. The type of respiratory support, mode of delivery, type of nebulizer used, and the location of the nebulizer within the mechanical ventilator circuit (if applicable) were collected. In addition, the tobramycin product used, indications for use, dosage regimen, duration, and monitoring considerations were collected.

The primary objective was to identify the number of respondents who use inhaled tobramycin in critically ill pediatric patients without CF in the NICU, PICU, and CICU. The secondary objectives included the main indications, dosage regimens, and monitoring parameters used. An additional secondary objective was to identify administration details for inhaled tobramycin, including the type of respiratory support, mode of delivery, type of nebulizer used, and the location of the nebulizer within the mechanical ventilator circuit.

All investigators developed and reviewed the questionnaire to ensure its face validity. In addition, informal feedback was obtained from 2 pediatric pharmacists who serve on the PPA PBRN. Descriptive statistics, including frequencies and percentages, were used to summarize the survey responses using SAS, version 9.4 (SAS Institute, Inc., Cary, NC).

Results

During the study period, 159 respondents accessed the questionnaire. Of these entries, 80 were excluded for the following reasons: opened link but did not complete required questions (n = 76) and duplicate submission of information from the same institution (n = 4). Seventy-nine responses from 79 unique health systems

were included for analysis. An overall response rate of 25.5% was calculated from the 310 health systems represented by PPA members.

Demographics of Respondents Using Inhaled Tobramycin in NICU/PICU/CICU. Sixty-one (77.2%) of 79 respondents indicated that they use inhaled tobramycin for critically ill children without CF in 1 or more ICU. Table 1 provides an overview of the health system and demographics of the 61 institutions using inhaled tobramycin in their ICUs. Most respondents were from the United States in either the Southeast (n = 15/61; 24.6%) or West (n = 14/61; 23.0%). In addition, most respondents (n = 25/61; 41.0%) had 200 or more pediatric beds in their health system. The number of respondents that used inhaled tobramycin in their ICUs varied, including 37 respondents (60.7%) with 1 ICU type, 14 (23.0%) with 2 types of ICUs, and 10 (16.4%) with 3 types of ICUs. The ICU with the most usage of inhaled tobramycin was the PICU (n = 45, 73.8%), followed by the NICU (n = 36; 59.0%) and CICU (n = 14; 23.0%). There was variability in the number of beds in the NICUs, PICUs, and CICUs.

Inhaled Tobramycin Protocol Components. Most respondents (n = 73, 92.4%) indicated that their institution did not have an inhaled tobramycin protocol. There was variability in the ICU type that had a protocol. Table 2 summarizes the protocol and administration details for inhaled tobramycin by ICU type. The majority of PICUs (n = 25/45; 56.6%) and NICUs (n = 16/36; 44.5%) use 1 of the commercially available inhaled tobramycin products for nebulization solution that has an FDA-labeled indication for eradication of *Pseudomonas aeruginosa* in CF patients (TOBI; Novartis Pharmaceuticals Corporation, East Hanover, NJ; Bethkis, Cornerstone Therapeutics Inc., Woodstock, IN).[13,14] Some respondents noted that their ICUs use an intravenous tobramycin product either with or without preservatives for administration via nebulization, including the majority of CICUs (n = 10; 71.4%). Respondents were asked for indications for inhaled tobramycin, including for non-CF bronchiectasis, chronic colonization suppression, VAP, or VAT. There was variability in indication according to ICU type, with the highest indication among all ICUs for VAT (69.4%–77.8%).

Table 2 also summarizes the administration details of inhaled tobramycin according to ICU type. Most respondents (78.6%–88.9%, depending on the unit type) noted that inhaled tobramycin is administered in mechanically ventilated patients in their ICUs, with a smaller percentage of respondents (55.6%–66.7%) indicating that patients with high-frequency mechanical ventilation (e.g., high-frequency jet ventilator or high-frequency oscillatory ventilation) received inhaled tobramycin. For patients who are mechanically ventilated, most respondents noted that the endotracheal (90.0%–100%) or tracheostomy tube (66.7%–82.5%) were the main modes of delivery of inhaled tobramycin. Most respondents indicated that they were unaware of the nebulizer used and the location of administration within the mechanical ventilator circuit used to deliver inhaled tobramycin. The number of institutions using a vibrating mesh nebulizer ranged from 11.1% to 21.4%, depending upon ICU type. There were various responses from respondents who were aware of the delivery location in the ventilator circuit.

Table 1. Baseline Demographics of Health-Systems for Respondents Using Inhaled Tobramycin in Critically Ill Children Without Cystic Fibrosis

Variables	*N* (%)
Location of institutions:	
Northeast United States	10 (16.4)
Midwest United States	11 (18.0)
Southeast United States	15 (24.6)
Southwest United States	10 (16.4)
West United States	14 (23.0)
Outside of the United States	1 (1.6)
Number of pediatric hospital beds in the health system:	
50–99	17 (27.9)
100–149	10 (16.4)
150–199	9 (14.8)
≥ 200	25 (41.0)
Types of ICUs:	
NICU	36 (59.0)
PICU	45 (73.8)
CICU	14 (23.0)
Number of beds in NICU (n = 36):	
0–25	1 (2.8)
26–50	11 (30.6)
51–75	13 (36.1)
≥ 75	11 (30.6)
Number of beds in PICU (n = 45):	
0–25	27 (60.0)
26–50	14 (31.1)
51–75	3 (6.7)
≥ 75	1 (2.2)
Number of beds in CICU (n = 14):	
0–25	12 (85.7)
26–50	2 (14.3)
51–75	–
≥ 75	

CICU, cardiac intensive care unit; ICU, intensive care unit; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit

Tobramycin Dosage Regimen and Monitoring. Respondents were asked to indicate the dosage regimen and duration for all 4 indications (i.e., non-CF bronchiectasis, suppression of chronic colonization, VAP, or VAT). Because VAT was the most common indication noted among ICU units, the subsequent analysis was focused on VAT. There was variability in the dosage and duration of VAT (Table 3). For the NICU and CICU, the most common dosage regimens were 40 to 80 mg every 8 to 12 hours (NICU [n = 18; 72.0%]; CICU [n = 5; 38.5%]) or 150 mg every 12 hours (NICU [n = 4; 16.0%];

Table 2. Inhaled Tobramycin Protocol and Administration Considerations Among ICUs

Variables	PICU (n = 45)	NICU (n = 36)	CICU (n = 14)
		N (%)	
Inhaled Antibiotic Policy Information and Product Used			
Has policy for inhaled antibiotics in critically ill children without CF	6 (13.3)	3 (8.3)	2 (14.3)
Components included in policy:	n = 6	n = 3	n = 2
Indications for use	3 (50.0)	2 (66.7)	1 (50.0)
Administration details	4 (66.7)	2 (66.7)	1 (50.0)
Dosage regimen	4 (66.7)	3 (100.0)	2 (100.0)
Monitoring considerations	4 (66.7)	2 (66.7)	1 (50.0)
Tobramycin product most frequently used:			
Solution for injection (10 mg/mL preservative-free)	10 (22.2)	10 (27.8)	3 (21.4)
Solution for injection (10 or 40 mg/mL)	10 (22.2)	10 (27.8)	7 (50.0)
Solution for inhalation (TOBI)	23 (52.2)	15 (41.7)	4 (28.6)
Solution for inhalation (Bethkis)	2 (4.4)	1 (2.8)	–
Indication for inhaled tobramycin:			
Non-CF bronchiectasis	18 (40.0)	6 (16.7)	3 (21.4)
Suppression of chronic colonization	33 (73.3)	20 (55.6)	8 (57.1)
VAP	28 (62.2)	17 (47.2)	8 (57.1)
VAT	35 (77.8)	25 (69.4)	13 (92.9)
Respiratory Support and Mode of Delivery With Mechanical Ventilation Used with Inhaled Tobramycin			
Respiratory support:			
Mechanical ventilation	40 (88.9)	30 (83.3)	11 (78.6)
High-frequency mechanical ventilation	25 (55.6)	24 (66.7)	8 (57.1)
Noninvasive mechanical ventilation	31 (68.9)	24 (66.7)	10 (71.1)
Mode of delivery with mechanical ventilator:			
Endotracheal tube	36 (90.0)	30 (100.0)	11 (100.0)
Tracheostomy tube	33 (82.5)	20 (66.7)	9 (81.8)
Mouthpiece	6 (15.0)	4 (13.3)	1 (9.1)
Nebulizer and Location of Nebulizer With Mechanical Ventilator			
Type of nebulizer used with mechanical ventilator:			
Jet or compression	9 (20.0)	4 (11.1)	2 (14.3)
Ultrasonic	5 (11.1)	5 (13.9)	1 (7.1)
Vibrating mesh	5 (11.1)	5 (13.9)	3 (21.4)
Unknown	26 (57.8)	21 (58.3)	8 (57.1)
Location of nebulizer with mechanical ventilator circuit:	n = 40	n = 30	n = 11
Distal (i.e., on the inlet of the humidifier)	6 (15.0)	4 (13.3)	–
Proximal (i.e., between patient wye connector within inspiratory limb of ventilator circuit)	2 (5.0)	4 (13.3)	1 (9.1)
Between the wye connector and the endotracheal tube	1 (2.5)	–	1 (9.1)
Unknown	31 (77.5)	22 (73.3)	9 (81.8)

CF, cystic fibrosis; CICU, cardiac intensive care unit; ICU, intensive care unit; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit; VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheitis

CICU [n = 4; 30.8%]). The most common dosage regimen for VAT in the PICU was 300 mg every 12 to 24 hours (n = 13; 37.2%). Some respondents indicated that their ICUs adjust their dosage for patients with AKI (PICU [n = 8; 17.8%], NICU [n = 6; 16.7%], CICU [n = 6; 42.9%]). The most common duration noted for VAT among the ICUs was between 7 and 10 (45.7%–56.0%) and 11 and 14 days (17.1%–30.8%) (Table 3). However, a few respondents indicated that providers in their ICUs would use inhaled tobramycin every 14 or 28 days on and 14 or 28 days off instead of a defined duration.

Table 4 provides a summary of monitoring considerations with inhaled tobramycin among ICUs. There was a wide variability of renal function monitoring with serum creatinine while on inhaled tobramycin, with some monitoring daily and others not performing routine monitoring. A few respondents (8.9%–21.4%, depending on ICU type) indicated their ICUs monitor tobramycin

Table 3. Summary of Inhaled Tobramycin Dosing and Duration with VAT Among ICUs

Variables	PICU (n = 45)	NICU (n = 36)	CICU (n = 14)
		N (%)	
Number of ICUs using inhaled tobramycin for VAT	35 (77.8)	25 (69.4)	13 (92.9)
Dose:			
40–80 mg every 8–12 hours	11 (31.4)	18 (72.0)	5 (38.5)
150 mg every 12 hours	6 (17.1)	4 (16.0)	4 (30.8)
300 mg every 12–24 hours	13 (37.2)	1 (4.0)	2 (15.4)
Age and weight-dependent	2 (5.7)	1 (4.0)	2 (15.4)
Dosing not specified	3 (8.6)	1 (4.0)	–
Duration:			
1–6 days	7 (20.0)	1 (4.0)	1 (7.7)
7–10 days	16 (45.7)	14 (56.0)	7 (53.8)
11–14 days	6 (17.1)	8 (32.0)	4 (30.8)
15–21 days	1 (2.9)	–	–
14 days on and 14 days off	–	–	1 (7.7)
28 days on and 28 days off	2 (5.7)	1 (4.0)	–
Duration not specified	3 (8.6)	1 (4.0)	–

CICU, cardiac intensive care unit; ICU, intensive care unit; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit; VAT, ventilator-associated tracheitis

Table 4. Inhaled Tobramycin Monitoring Data by Unit

Variable	PICU (n = 45)	NICU (n = 36)	CICU (n = 14)
		N (%)	
Frequency of serum creatinine monitoring for patients on inhaled tobramycin:			
Daily	9 (20.0)	5 (13.9)	4 (28.6)
Every other day	2 (4.4)	1 (2.8)	–
Twice a day	5 (11.1)	8 (22.2)	2 (14.3)
Once weekly	6 (13.3)	9 (25.0)	1 (7.1)
Not routinely performed	18 (40.0)	11 (30.6)	7 (50.0)
No response provided	5 (11.1)	2 (5.6)	–
Monitor tobramycin concentrations routinely	4 (8.9)	6 (16.7)	3 (21.4)
Timing of initial tobramycin concentration:	n = 4	n = 6	n = 3
Before 2–4 dose	2 (50.0)	4 (66.6)	1 (33.3)
Only in patients with acute kidney injury	2 50.0)	1 (16.7)	–
Varies based on provider discretion	–	1 (16.7)	–
Timing of subsequent concentrations:	n = 4	n = 6	n = 3
Weekly	1 (25.0)	1 (16.7)	1 (33.3)
No subsequent concentrations unless concerns for acute kidney injury	2 (50.0)	3 (50.0)	1 (33.3)
Varies based on provider discretion	1 (25.0)	2 (33.3)	1 (33.3)
Serum concentration tobramycin dose decreased or discontinued:	n = 4	n = 6	n = 3
No threshold established	1 (25.0)	1 (16.7)	–
≤ 0.5 mcg/mL	1 (25.0)	2 (33.3)	1 (33.3)
≥ 1 mcg/mL	1 (25.0)	2 (33.3)	1 (33.3)
< 2 mcg/mL	1 (25.0)	1 (16.7)	1 (33.3)

CF, cystic fibrosis; CICU, cardiac intensive care unit; ICU, intensive care unit; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit

serum concentrations while receiving inhaled tobramycin. Of those respondents who monitored tobramycin serum concentrations, some indicated it was before the second to fourth inhaled tobramycin dose, while others indicated it was only in patients with AKI at baseline. In addition, there was a variety of responses for subsequent tobramycin serum concentration monitoring, with some performing weekly monitoring and others

based on provider discretion. For those who perform tobramycin serum concentration monitoring, there was a variety of responses with some indicating their goal concentration in which they reduced or discontinued the tobramycin was ≥ 0.5 to 2 mcg/mL and others who had no established threshold.

Discussion

To our knowledge, this is the first survey exploring the use of inhaled antibiotics in children without CF in pediatric-specific health systems. While the 2016 IDSA guidelines for hospital-associated pneumonia or VAP recommend inhaled antibiotics for multidrug-resistant organisms, there remains a paucity of studies evaluating inhaled tobramycin in critically ill children.[1] In pediatric patients, most of the data surrounding the use of inhaled tobramycin is in patients with CF. As previously noted, tobramycin is available in 2 commercially available solutions for inhaled use, TOBI (300 mg/4 mL) and Bethkis (300 mg/5 mL), and both agents have an FDA-approved labeled indication for eradication of *P. aeruginosa* for CF children 6 years of age and older.[15] Additionally, the Cystic Fibrosis Foundation has also recommended its use in children older than 6 months to 5 years of age.[16] Several case reports or studies have explored the use of inhaled tobramycin for off-label indications in adults and children without CF.[3–8,11,17–19] However, not all of these studies have explored the use of inhaled tobramycin in critically ill patients who are mechanically ventilated, particularly because there is concern regarding the disposition of inhaled tobramycin in the ventilator circuit. We noted that most respondents (n = 61; 77.2%) use inhaled tobramycin in critically ill children without CF for off-label indications, including non-CF bronchiectasis, chronic colonization suppression, VAT, and/or VAP. Despite the small sample, these findings may provide the pediatric pharmacy community with insight into the tobramycin product most commonly used, the nebulizer used for its administration, and monitoring considerations (serum concentrations and lung function) for inhaled tobramycin. The findings in the present study will be used to develop additional studies aimed at outlining the parameters that are critical to ensure the efficacy and safety of inhaled antibiotics in critically ill children and, in the future, to propose a standard protocol to guide the treatment of patients in the NICU with inhaled antibiotics

Most respondents (92.4%) indicated that their institution did not have a standardized protocol for inhaled tobramycin in their ICUs. As previously noted, several studies evaluating inhaled tobramycin have noted between 8.3% and 68.2% of critically ill adults and children with detectable tobramycin serum concentrations.[7–11] It is possible that standardization of the tobramycin product used, dose, the nebulizer used, and administration details within the ventilator circuit may limit systemic toxicities, including AKI with inhaled tobramycin. Most of the published studies evaluating the use of inhaled tobramycin in critically ill patients do not elucidate all these details.[7–10]

Variability was observed in the inhaled tobramycin product administered in the ICUs, with most PICU and NICU respondents using commercially available solutions, such as TOBI or Bethkis, while others administered intravenous tobramycin solution via nebulizer. Previous studies evaluating inhaled tobramycin in critically ill children and adults have used the TOBI product[7,10,11] or the 40 mg/mL intravenous tobramycin formulation.[8,9] The tobramycin product selected may have some impact on absorption and adverse events with inhaled administration. The airway epithelium has a pH of around 5 to 6, and both TOBI and Bethkis are pyrogen-free and sterile solutions that are buffered to match the pH of airway epithelium.[13,14,20] In contrast, intravenous tobramycin has a pH ranging from 3 to 6.5.[21] It is possible that the increased acidity of the intravenous tobramycin solution may cause damage to the airway epithelium and lead to increased or decreased absorption compared with the buffered tobramycin solutions. We also noted several institutions that used the 10 or 40 mg/mL intravenous tobramycin solutions that contain preservatives (Table 2). Experts caution against the use of solutions that contain preservatives as they may cause airway irritation and increase the risk of bronchospasm.[20]

Respondents were asked several questions regarding the nebulizer, mode of delivery of inhaled tobramycin, and placement within the ventilator circuit. Overall, the most common modes of delivery were the endotracheal tube followed by the tracheostomy tube. In the 3 studies evaluating inhaled tobramycin in 96 critically ill children, most patients received tobramycin via a tracheostomy tube (n = 74; 77.1%) compared with endotracheal tubes (n = 21; 21.9%).[7,8,11] This is likely because most of these patients may have received inhaled tobramycin for VAT. Most respondents indicated using inhaled tobramycin in patients receiving noninvasive ventilation, but fewer respondents reported use for patients requiring high-frequency mechanical ventilation. This may reflect the fact that there are limited data about the disposition of inhaled antibiotics in high-frequency mechanical ventilation and additional safety considerations when administering these medications.[1,20] In our study, most respondents were unaware of the nebulizer used and the location of the nebulizer within the ventilator circuit. For mechanically ventilated patients, experts recommend the use of vibrating mesh nebulizers as the preferred nebulizer as they are more efficient than jet, compression, or ultrasonic nebulizers.[1,20] Additionally, it is recommended that the nebulizers are connected approximately 15 to 40 cm proximal to the mechanical ventilator (i.e., between the wye connector within the inspiratory limb of

the ventilator circuit) to enhance medication delivery.[1] The fact that so many respondents were unaware of the nebulizer used and the location of the nebulizer within the ventilator circuit may reflect that their institution has not established a preferred nebulizer or ventilator set up or perhaps a lack of pharmacist involvement. Given the concerns for either diminished or enhanced delivery of inhaled medications, we recommend that clinical pharmacists work with their providers and respiratory therapy colleagues to ensure appropriate administration techniques to increase efficacy while limiting adverse effects.

Respondents noted a variety of dosage regimens and durations of inhaled tobramycin based on the indication for use. Owing to the considerable variability, our analysis focused on VAT because it was the most common indication noted by respondents. The most common dosage regimens for VAT were 40 to 80 mg every 8 to 12 hours or 150 mg every 12 hours. Previous studies have published a variety of dosage regimens used for non-CF critically ill children ranging from 40 to 300 mg/dose at intervals of every 8 to 12 hours.[7,8] For patients older than 6 months with CF, the recommended dose is 300 mg every 12 hours for 28 days in an on-and-off cycle.[13–15] However, there is a paucity of pharmacokinetic data in children younger than 6 months of age.[11,12,16] So, it is possible that respondents with NICUs and CICUs may use lower doses due to the lack of pharmacokinetic and safety data.

One study evaluating the incidence of detectable concentrations in critically ill children receiving TOBI 300 mg every 12 hours found 68.2% with detectable concentrations less than 0.5 mcg/mL.[11] In contrast, Hughes and colleagues[8] evaluated the concentrations of 12 critically ill children receiving inhaled tobramycin 80 mg every 8 hours using the 40 mg/mL intravenous tobramycin formulation and found 1 (8.3%) child with detectable serum concentrations, which they defined as < 0.6 mcg/mL. Given the limited sample size and the use of an intravenous tobramycin formulation not buffered to match the pH of the respiratory epithelium, determining an optimal dose for inhaled tobramycin remains challenging. This highlights a significant gap in our understanding and underscores the need for future studies to undertake comprehensive pharmacokinetic analyses of the tobramycin regimen.

The limited routine monitoring for detectable tobramycin serum concentrations reported by respondents is troubling, especially considering previous research that found between 8.3% and 68.2% of critically ill adults and children exhibited detectable serum concentrations of the drug.[7–11] Several of these studies have attempted to determine risk factors for detectable concentrations, but there remains a paucity of data on which patients may have the greatest risk. Compounding these concerns is the notable variability in how frequently ICUs monitor renal function despite evidence suggesting that up to 24% of patients with detectable serum concentrations may develop AKI.[7–11] Based on the findings in our study, we recommend pediatric clinical pharmacists work with interprofessional team members to ensure monitoring components are included in developing policies or protocols for inhaled tobramycin.

This study has several limitations that must be addressed. First, it has a limited response rate of only one-quarter of pediatric institutions represented by members of the PPA. Despite this, the study did include respondents from across the United States who practice at institutions with a variety of bed sizes. Second, the questionnaire used in this study was not validated. As a result, some respondents may have been confused when answering questions. We did address face validity by obtaining feedback from 2 practicing pediatric pharmacists affiliated with the PPA PBRN. Third, though we asked respondents several questions about the administration of tobramycin through several types of nebulizers, we did not have a question about age restrictions for these nebulizer devices. Several of the nebulizers may have FDA-labeled indications for young infants and neonates.

Conclusions

This study noted that most respondents used inhaled tobramycin in their ICUs, but most did not have a standardized protocol for use in critically ill children without CF. There was substantial variability in the nebulizers used, position with the ventilator circuit, dosage regimen, and monitoring considerations among the ICUs of respondents. This study highlights opportunities for pediatric clinical pharmacists to work with interprofessional teams, including respiratory therapists and providers, to standardize the use of inhaled antibiotics like tobramycin. Additionally, these findings may provide a foundation for future prospective, multicenter studies investigating the use of inhaled tobramycin for critically ill children for a variety of indications, including VAT and VAP.

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Disclosure. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript,

including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors attest to meeting the four criteria recommended by the ICMJE for authorship of this manuscript.

Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and has been approved by each institution's review board. Given the nature of this study, informed consent, assent, and parental permissions were not required.

Acknowledgment. At the time of this study, Dr. Ropp was a PGY1 Pharmacy Resident at the University of Oklahoma College of Pharmacy and OU Health.

Submitted. June 18, 2024

Accepted. August 15, 2024

Supplemental Material. DOI: 10.5863/JPPT-24-00061.S1

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