# Systemic Aminoglycoside Accumulation from Inhaled Tobramycin in Tracheostomy-Dependent Children with Congenital Cardiac Disease

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## Background

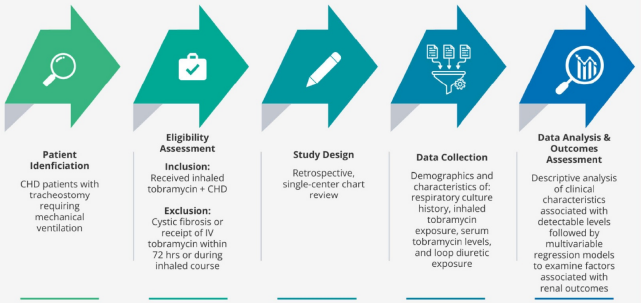
- Children with congenital heart disease (CHD) who require tracheostomy with mechanical ventilation are at high risk for recurrent respiratory infections
- Nebulized antimicrobials, including tobramycin, are frequently used off-label with aims to suppress airway pathogens, but data are limited to cystic fibrosis
- Current practices do not encourage or support serum level monitoring of inhaled tobramycin
- Several studies have shown pediatric patients may experience substantial systemic absorption from inhaled tobramycin therapy[1-6]
- Understanding risk associated with potential systemic absorption and accumulation during ongoing inhaled tobramycin cycling is crucial for safe clinical practice[7, 8]
- Anecdotal data from our center illustrates high incidence of detectable, potentially toxic, tobramycin serum levels in tracheostomy-dependent children with CHD

## Study Objective & Aim

- **Objective:** Identify factors associated with detectable levels of inhaled tobramycin in trach/vented infants and young children with CHD
- **Aim:** Share our center's experience with systemic absorption of inhaled tobramycin to help guide and encourage future literature focusing on pharmacokinetics in pediatric cardiac populations

## Methods

**Figure 1.** Study design and data collection workflow for tracheostomy-ventilated patients with congenital heart disease receiving inhaled tobramycin.




## Results

- A total of 80 serum tobramycin concentrations were obtained of which 64 (80%) had detectable serum tobramycin levels and 16 (20%) had undetectable levels suggesting systemic accumulation which is not an expected finding
- Demographic characteristics were largely similar between groups
- Detectable serum tobramycin concentrations were associated with (Tables 1, 2):
  - **Longer treatment duration**
  - **Higher weight-based & cumulative dosing**
  - **Use of positive pressure ventilation**

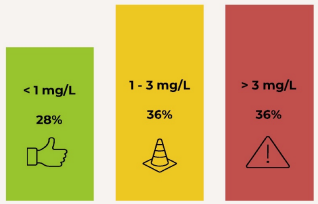



**Figure 2.** Distribution of serum levels within detectable group where goal is undetectable by assay or at minimum < 1 mg/dL.

***Table 1. Serum Tobramycin Measurement-Level Data by Detectability with Mixed-Effects Comparisons***

| Variable | Undetectable (<0.5 mg/dL) n = 16[1] | Detectable (≥0.5 mg/dL) n = 64[1] | Mixed model effect (95% CI) | Mixed model p-value |
|---|---|---|---|---|
| **Dose (mg/dose)** | — | — | 49.83 (14.74 to 84.92) | **0.006** |
| 22.5 | 3 (19%) | 5 (7.8%) | 49.83 (14.74 to 84.92) | **0.006** |
| 37.5 | 6 (38%) | 7 (11%) | 49.83 (14.74 to 84.92) | **0.006** |
| 82.5 | 5 (31%) | 33 (52%) | 49.83 (14.74 to 84.92) | **0.006** |
| 150 | 2 (13%) | 5 (7.8%) | 49.83 (14.74 to 84.92) | **0.006** |
| 300 | 0 (0%) | 14 (22%) | 49.83 (14.74 to 84.92) | **0.006** |
| **Weight-based dose (mg/kg/dose)** | 3.4 [3.4, 9.9] | 11.8 [9.0, 22.7] | 6.67 (2.15 to 11.19) | **0.004** |
| **Time level attained post-dose (hours)** | 10.5 [5.9, 11.4] | 11.4 [8.4, 18.2] | 4.72 (-5.89 to 15.33) | 0.378 |
| **Days into tobramycin course** | 3.4 [2.2, 5.0] | 6.0 [3.5, 9.5] | 2.80 (1.16 to 4.43) | **0.001** |
| **Positive pressure ventilation** | 15 (94%) | 64 (100%) | — | — |
| **Serum creatinine at baseline (mg/dL)** | 0.3 [0.2, 0.3] | 0.3 [0.2, 0.4] | 0.02 (-0.03 to 0.06) | 0.441 |
| **eGFR at baseline (mL/min/1.73 m²)** | 108.0 [108.0, 156.5] | 82.3 [70.1, 128.0] | -1.15 (-8.43 to 6.13) | 0.753 |
| **Serum creatinine at level attainment (mg/dL)** | 0.3 [0.2, 0.3] | 0.4 [0.3, 0.7] | 0.06 (-0.11 to 0.24) | 0.459 |
| **Change in creatinine from baseline (mg/dL)** | 0.0 [0.0, 0.0] | 0.1 [0.0, 0.3] | 0.05 (-0.12 to 0.22) | 0.564 |
| **eGFR at level attainment (mL/min/1.73 m²)** | 108.0 [94.0, 156.5] | 74.2 [40.8, 108.0] | -10.19 (-20.98 to 0.59) | 0.064 |
| **Change in eGFR from baseline (mL/min/1.73 m²)** | 0.0 [-5.5, 1.1] | -26.9 [-48.0, 0.0] | -11.75 (-22.85 to -0.65) | **0.038** |
| **7-day loop diuretic exposure (mg PO furosemide equiv.)** | 20.0 [20.0, 65.0] | 48.0 [0.0, 276.0] | 24.16 (-20.99 to 69.32) | 0.288 |
| Missing | 1 | 7 | 24.16 (-20.99 to 69.32) | 0.288 |
| **7-day loop diuretic exposure (mg/kg)** | 1.8 [1.8, 9.5] | 8.0 [0.0, 32.5] | 2.69 (-2.53 to 7.90) | 0.307 |
| Missing | 1 | 7 | 2.69 (-2.53 to 7.90) | 0.307 |

n (%); Median [Q1, Q3]

**Table 2. Predictors of log(Tobramycin Level): Univariable and Adjusted Linear Mixed Models**

| | Univariable | | | Adjusted | | |
|---|---|---|---|---|---|---|
| **Characteristic** | **β (95% CI)** | **95% CI** | **p-value** | **β (95% CI)** | **95% CI** | **p-value** |
| **Dose (mg/kg/dose)** | 0.05 | 0.02, 0.07 | **<0.001** | 0.04 | 0.02, 0.07 | 0.002 |
| **Baseline creatinine** | 0.80 | -1.8, 3.4 | 0.5 | 1.2 | -1.5, 3.9 | 0.4 |
| **Time post dose (hours)** | -0.01 | -0.02, 0.00 | 0.082 | -0.02 | -0.03, 0.00 | **0.009** |
| **Days into tobramycin course** | 0.05 | -0.03, 0.13 | 0.2 | 0.08 | -0.01, 0.16 | 0.075 |
| **Pre-existing renal disease** | | | | | | |
| *No* | — | — | | — | — | |
| *Yes* | 0.44 | -0.57, 1.5 | 0.4 | 0.27 | -0.73, 1.3 | 0.6 |

*Abbreviation: CI = Confidence Interval*
*No. Obs. = 80; Sigma = 0.881*

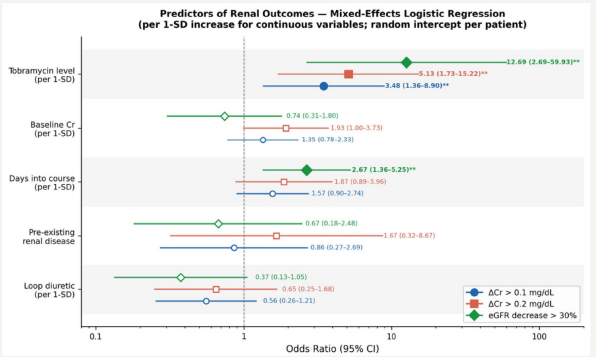



**Figure 3.** Mixed-effects logistic regression with predictors of renal outcomes. ORs per 1-SD for continuous variables. Filled symbols = p < 0.05; open symbols = p ≥ 0.05 (*p<0.05, ** p<0.01, *** p<0.001).

## Conclusions

- Detectable serum tobramycin levels were obtained from most subjects suggesting systemic accumulation which is not expected and appears to be unprecedented in both degree and clinical context
- Each standard deviation increase in tobramycin serum concentration is associated with 12.7x increased risk of a >30% decrease in eGFR consistent with dose-dependent downstream nephrotoxic effects
- Data from other pediatric populations are not generalizable to this cohort

## Future Directions

- Prospective trials of tobramycin inhalation pharmacokinetics in CHD
- Pharmacokinetic modeling for patient-specific dosing
- Development of dosing and monitoring guidelines

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