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Factors Associated with Ototoxicity among TB Patients Treated with Aminoglycosides

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2016

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An abstract of

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology

2018

Abstract

Factors Associated with Ototoxicity among TB Patients Treated with Aminoglycosides

By Gillian Smith

Multi-resistant tuberculosis (MDR TB) has become a persistent threat to the elimination of TB and requires lengthy, expensive and often toxic treatment. There were an estimated 600,000 cases of MDR TB worldwide in 2016. Aminoglycosides are an important class of drugs in MDR TB treatment, but are known to be highly nephrotoxic and ototoxic (hearing loss). The association between aminoglycoside treatment for TB and ototoxicity is not well studied and this paper seeks to fill in this knowledge gap.

This paper is a secondary analysis of patients hospitalized for TB treatment at the Tuberculosis Unit of the University of Texas Health Science Center (UTHSCT), Texas Center for Infectious Diseases (TCID) and A.G. Holley Hospital (AGHH), Lantana, Florida. The dataset for this study included all patients with therapeutic drug monitoring and at least 2 audiograms. Serial audiogram measurements were used to conduct a longitudinal multivariate analysis of the association between cumulative dosage of aminoglycosides and ototoxicity, using generalized estimating equations.

We report an incidence of ototoxicity of 33.3% (n = 27) in the study population. The odds of ototoxicity was 3.75 times higher among patients with a cumulative dosage of any aminoglycoside greater than 131 grams compared to a cumulative dosage less than or equal to 131 grams (95% CI 1.42,9.96, p = 0.01). Gender, history of TB and total duration of aminoglycoside treatment were also associated with an increased odds of ototoxicity (p = 0.03, p = 0.09, p = 0.04). The odds of ototoxicity was 6.23 times higher among patients at UTHSCT than patients at TCID/AGHH (95% CI 1.5, 25.77, p = 0.02).

Cumulative dosage of aminoglycosides greater than 131 grams is associated with increased odds of ototoxicity. The threshold may biologically represent a threshold of accumulation of aminoglycosides in cochlear cells where cell death is inevitable. Providers should consider carefully and routinely monitoring the level of total exposure to aminoglycosides among patients and perform regular hearing evaluations. However, further study of aminoglycoside-induced ototoxicity is necessary to understand the risk for patients receiving TB treatment before treatment guidelines can be changed.

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BACKGROUND

Active tuberculosis (TB) is a disease caused by the bacteria *Mycobacterium tuberculosis*. It is transmitted from person-to-person through the air. Upon infection, patients typically go through a stage referred to as Latent TB Infection (LTBI) where the mycobacterium may form granulomas and stay dormant. A patient with LTBI is asymptomatic and not able to transmit TB (1). It is thought that approximately 10% of infected persons will develop an active TB disease. During active TB disease patients typically experience fever, fatigue, lack of appetite and weight loss, persistent cough and hemoptysis (2). The majority of TB cases occurs in the lungs, but the disease can occur throughout the body.

M. tuberculosis has been causing disease for thousands of years. Descriptions of it have been found in ancient writings from Egypt, India, Greece and even among Charles Dickens writings (3). At the start of the 20th Century, annual mortality from TB was around 200 per 100,000 population worldwide (4). In 2016, TB incidence was estimated to be almost 140 per 100,000 or 10.4 million new cases (3). The global estimate of TB mortality was 17 per 100,000 for HIV-negative persons and 5 for HIV-positive persons. While this represents a significant decrease in TB cases and improvement in treatment, it remains among the top ten causes of death and the top infectious cause of death worldwide. In the highest burden countries the mortality can reach 75 per 100,000 among HIV-negative persons and 238 per 100,000 persons among HIV-positive persons.

TB TREATMENT AND DRUG-RESISTANT TB

The majority of TB cases are considered to be drug-susceptible, which means there is no known or suspected resistance to the first line anti-TB drugs. For drug-susceptible TB, the recommended treatment protocol in the United States (US) and globally is isoniazid, rifampin, pyrazinamide and ethambutol for 2 months followed by isoniazid and rifampin for 4 additional months (4). The

global standard of care is to administer the drugs under Directly Observed Therapy (DOT) 5 days a week at the healthcare facility, at a patients' home, or "field" locations by trained personnel. DOT, directly observing patients swallowing their antibiotics, can help ensure adherence to the long and often difficult treatment protocols. The initial treatment regimen includes these 4 drugs due to the levels of isoniazid resistance of up to 14% among previously treated cases worldwide (5,6). The objective of treatment for TB is to ensure at least 3 effective drugs are used. TB strains that are resistant to at least both isoniazid and rifampin are referred to as multidrug-resistant TB (MDR TB).

MDR TB has become a persistent threat to the efforts to eliminate TB. There were an estimated 600,000 cases of drug-resistant TB worldwide and 97 cases in the US in 2016 (5,7). Although these cases represent only approximately 6% of cases worldwide and 1.4% of culture-positive cases in the US, they require lengthy regimen of toxic and expensive drugs and carry high mortality rates (8). As MDR TB cases are resistant to at least 2 of the first-line drugs, isoniazid and rifampin, treatment regimens for MDR TB must include second-line anti-TB drugs. The second-line drugs are categorized in 5 separate groups as seen in Table 1. Ideal selection of treatment regimens for persons with MDR TB depend on the resistance pattern of the individual and in the country as a whole. The World Health Organization (WHO) recommends using at least 4 drugs known to be susceptible that include one from groups 1-4. Common practice is to have an initial 6 month regimen including an injectable agent, which requires administration by a skilled health care worker, followed by a second 12-18 month regimen of at least 4 drugs given orally. A common standard regimen in some countries includes kanamycin, ofloxacin, ethionamide, pyrazinamide and either cycloserine, ethambutol or both (9–12). A shorter regimen of kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, high-dose isoniazid and ethambutol for 4-6 months, followed by 5 months of moxifloxacin, clofazimine and ethambutol has been proposed if patients are susceptible to all drugs in the regimen (13).

Table 1. Second-line drugs used for treatment of multi-drug resistant tuberculosis (MDR TB).

Group	Category	Drugs
1	First-line oral agents	Ethambutol, Rifubutin ,Pyrazinamide
2	Injectable agents or aminoglycosides	Kanamycin, Amikacin, Capreomycin, Streptomycin
3	Fluoroquinolones	Ofloxacin, Moxifloxacin, Levofloxacin
4	Oral bacteriostatic second-line agents	Para-aminosalicylic acid (PAS), Cycloserine, Terizidone, Ethionamide, Protionamide
5	Agents with unclear role in treatment	Clofazimine, Linezolid, Amoxicillin, Thioacetazone, Cilastatin High-dose isoniazid, Clarithromycin

It has been used in 14 countries, mainly in Africa, with promising results. In the United States, guidelines jointly developed by the American Thoracic Society (ATS), CDC, and Infectious Diseases Society of America (IDSA) suggest expert consultation be used to design an appropriate regimen in the event of MDR TB(6). These guidelines support the use of treatment regimens previously published by the European Respiratory Society (14).

AMINOGLYCOSIDES

Mechanisms of Action

Aminoglycosides are bactericidal antibiotics which work by targeting bacterial ribosomes' 30S subunit causing disruption of protein synthesis (15). Accumulation of nonfunctional proteins eventually causes bacterial death. They typically have poor oral absorption so they require parenteral administration, commonly by intramuscular (IM) or intravenous (IV) injection.

Application to non-TB Diseases

Aminoglycosides are broadly used for infections caused by gram negative bacteria other than tuberculosis. They are considered first line drugs for treatment of persons with plague, tularemia, *bartonella* infections, leishmaniasis, listeria, brucellosis and endocarditis from gram-positive cocci and gram-negative bacilli (16). Aminoglycosides are also used in some cases of sepsis, urinary tract infections, meningitis, *Pseudomonas aeuroginosa* infection in cystic fibrosis (CF) and in hemodialysis patients.

Application to TB

Streptomycin (S) was found to be the first medication to effectively kill the tuberculosis mycobacterium in the mid 1940's (3). It was shown to be effective in humans in a few randomized control trial comparing high-dose strepromycin monotherapy with no treatment or p-aminosalicylic acid (PAS) (17). However, streptomycin was also quickly found to be toxic to the kidneys (nephrotoxicity) and cause hearing loss (ototoxicity) in many patients. In spite of the toxicity, aminoglycosides continued to be used alongside PAS and isoniazid (INH) until 1957 when rifampin (RIF) was discovered as an effective and less toxic alternative. In 1968, this new drug received approval for therapeutic use in combination with other drugs. With the emergence of MDR TB aminoglycosides have become an important part of TB drug regimens again. Three cohort studies which showed that susceptibility to aminoglycosides in MDR TB patients was associated with better outcomes provide the basis of evidence for its use in MDR TB treatment (18–20). Streptomycin is more commonly replaced by amikacin (AM), kanamycin (KM), or capreomycin (CM). They have increasingly caused concern over their inclusion in the MDR TB regimen due to their high toxicity and pain at injection (17).

Adverse Effects of Aminoglycosides

The toxicity of aminoglycosides has been well documented and has been connected associated with nephrotoxicity, electrolyte abnormalities, pain at the injection site, vestibular toxicity and ototoxicity (17). Nephrotoxicity and electrolyte abnormalities are common side effects among patients treated with aminoglycosides for TB and for other disorders. Nephrotoxicity is typically treatable and reversible but can be life-threatening if renal replacement therapy is limited. Ototoxicity, hearing loss, is considered to be the more serious of the adverse effects because it is typically permanent. Vestibular toxicity occurs through the same mechanism as ototoxicity but is thought to be less serious as it does not lead to hearing loss.

OTOTOXICITY

Aminoglycosides primarily target bacterial ribosomes but can also affect the mitochondria in cochlear hair cells (21). There are multiple potential pathways for the aminoglycosides to enter the hair cells, but limited pathways for aminoglycosides to leave hair cells. As they are not easily able to exit the cell, aminoglycosides build up in the cochlea. Animal studies have detected them in the cochlea within minutes of injection and over 30 days later (21–23). The long half-life and limited ability to exit cells cause accumulation of the aminoglycoside in the hair cells, where they generate reactive oxygen species (ROS). The ROS disrupt mitochondria and cause apoptotic cell death (17,21,22). The cell death is permanent leading to hearing loss. The resulting hearing loss is typically permanent, but there have been reports of improvement in hearing after stopping treatment in TB patients (24).

Ototoxicity is diagnosed through pure-tone audiometry (PTA), which measure the decibels (dB) of sound perceptible over a range of frequencies. Normal hearing levels typically fall within 20-30 dB. Ototoxicity is typically defined as a change of 20 dB at any one frequency or 10 dB at consecutive frequencies. It is typically identified at higher frequencies (4000-8000 Hertz (Hz)) before it affects the lower speech frequencies (250-3000 Hz) (15,25). The hearing loss is typically bilateral, but it has been reported as unilateral loss in rare cases (26,27). During TB treatment hearing loss is typically detected after months of treatment, but it has been detected in patients with aminoglycoside treatment for acute infections for 5-7 days (15).

Ototoxicity in non-TB Diseases

Patients with cystic fibrosis (CF) experience recurring *P. aeruginosa* infections throughout their lifetime, and therefore are often treated with aminoglycosides (AGs). Multiple studies have been conducted to investigate ototoxicity among these patients, the majority of which are children under 16 years. A study in 2011 of 48 children (4-16 years) receiving treatment at a specialty CF clinic in the United Kingdom found an incidence of aminoglycoside-induced ototoxicity of 35% (28). Patients were given either amikacin (AM) or tobramycin at 30 mg/kg and 10 mg/kg,

respectively. The participants were split into 3 exposure groups: no aminoglycoside exposure, low aminoglycoside exposure (≤ 5 courses of intravenous (IV) AG) and high aminoglycoside exposure (> 5 courses of IV AG). Only the high exposure group experienced ototoxicity. An additional study conducted among 70 CF patients (4-16 years) receiving amikacin, tobramycin or vancomycin in the same clinic further supported these results (29). The researchers defined again defined 3 exposure groups and increased the cutoff for high exposure to 10 or more courses of IV AG over their lifetime. The researchers identified an overall prevalence of ototoxicity 24% using high-frequency PTA. The prevalence was significantly higher in the high prevalence group (44%) compared to the low prevalence group (10%). Patients with ototoxicity had a median of 21 (range 3-40) courses of IV AG compared to patients without ototoxicity who had a median of 4 (range 0-31) courses of IV AG ($p<0.001$). A study in 1991 among 43 adult CF patients aged 14-42 years in Ireland reported a 16% prevalence of ototoxicity, defined as an increase of >30 dB on PTA (25). Patients were expected to have been exposed to aminoglycosides throughout their lifetime, although lifetime exposure was not measured. Serum concentrations were routinely monitored and only 2 of the 7 patients experiencing ototoxicity had levels that are considered toxic. The researchers posited that the lack of toxic serum levels may be due to existing hearing loss or a different biological response to aminoglycosides among CF patients. The decreased prevalence compared to reported prevalence in children may be a result of the higher cutoff for ototoxicity. However, a cohort study conducted among 39 adults (≥18 years) with CF in Chicago, Illinois found a similar level of ototoxicity: only 7 (18%) patients treated with either AM, tobramycin or gentamicin had hearing loss (30). Few risk factors were identified for ototoxicity in these studies, but increased age and Hispanic race were found to be significantly associated (29,30). Peak and trough serum level were examined as a risk factor in both studies, but only trough concentrations in the study in Chicago was significant (OR = 23.3, 95% CI 1.9-2.8; $p = 0.01$). Diabetes status, renal dysfunction, number of courses and concomitant NSAIDS were also explored as risk factors but were not statistically significant (30).

Treatment of non-tuberculosis *mycobacterium* (NTM) with aminoglycosides has also been shown to be associated with ototoxicity. In a retrospective cohort study in Australia, 8 (18%) patients being treated with IV amikacin for pulmonary NTM developed ototoxicity (31). The study followed 45 patients who were treated with thrice-weekly amikacin for 8 weeks at 22 mg/kg/day. This dose is higher than is used for TB treatment, but it was administered with lower frequency. In contrast, a small study conducted among 13 persons with NTM in Japan did not identify any ototoxicity in their cohort (32). The authors attribute the lack of ototoxicity to the low dosage of amikacin given to patients in the study (12.5 mg/kg thrice weekly for 3-9 months). Further, a randomized trial in Ghana from 2006-2009 comparing different dosages and duration of aminoglycosides for treatment of Buruli ulcer caused by *Mycobacterium ulcerans,* a NTM, also reported ototoxicity (33). Forty-one adults and 86 children (5-16 years) were randomized to two groups: 1) 8 weeks of streptomycin (15 mg/kg), or 2) 4 weeks of streptomycin and 4 weeks of clarithromycin (7.4 mg/kg) (a macrolide antibiotic). After 8 weeks, 13 adults (31%) and 23 (27%) children had ototoxicity defined through audiometry. Ototoxicity occurred in both treatment groups but in adults was significantly higher in the group that received 8 weeks of streptomycin ($p = 0.03$). Ototoxicity among children was statistically similar in both treatment arms.

Ototoxicity associated with aminoglycoside use for other indications has not been well studied, but there have been reports of ototoxicity among patients receiving aminoglycoside treatment during dialysis (34,35). In a study of 14 children (3-17 years) receiving long-term peritoneal dialysis in Kansas City, Kansas, 4 (44%) experienced ototoxicity (34). The patients that experienced hearing loss, defined as an increase of 20 dB at one frequency or 15 dB at any two frequencies on PTA, had all received previous IV aminoglycosides. Patients that only received peritoneal aminoglycosides did not experience hearing loss. In 103 adults (>18 years) in Turkey receiving peritoneal dialysis, ototoxicity was identified in 64% of patients who had previously

had peritonitis (35). In patients without previous peritonitis, only 24% of patients experienced hearing loss. Through multivariate regression, the authors found age and total amikacin dosage were significant risk factors for ototoxicity ($p = 0.001$, $p = 0.001$). Aminoglycosides have also been used as "locks" to prevent catheter-related infections during dialysis (36). It was believed that this use would not lead to ototoxicity because the aminoglycosides were delivered as catheter-restricted small quantities (5 mg/ml of gentamicin or 10 milligrams (mg)/milliliter (ml) of AM). However, ototoxicity has also been reported among patients receiving the "locks" (36,37) One reported case occurred in a 43-year old man from Saudi Arabia with diabetic nephropathy (36). The lock used during his hemodialysis was AM 3 days/week; he was also being treated with isosorbide dinitrite, aspirin and furosemide. After 16 weeks he reported hearing loss.

OTOTOXICITY IN TB

The risk of ototoxicity in CF patients is not directly translatable to the risk of ototoxicity in TB patients as CF patients often have higher dosage and lifetime exposure to aminoglycosides. CF patients also have greater volume of distribution and clearance rates of aminoglycoside (38). Aminoglycosides are also typically delivered parenterally for CF and not through injection or IV as they are for TB; parenteral administration is believed to have a lower risk of ototoxicity. Therefore, the prevalence of ototoxicity in TB patients may be expected to be higher than the prevalence of ototoxicity in CF. However, the reported prevalence and incidence of ototoxicity in TB patients varies widely (Table 2).

A study in Botswana of 437 MDR TB patients found a 62% incidence (n=271) of hearing loss following a treatment regimen containing amikacin (19). Over half (n=147; 54%) had confirmed hearing loss based on audiometry (change in 15 dB at 2 or more frequencies or 20 dB at any one frequency); the remaining cases of ototoxicity were based on self-reported hearing loss. Duration and cumulative dose of amikacin were found to be a significant predictor of ototoxicity in this cohort as well as an additional study of 28 MDR TB patients with serum monitoring of amikacin

levels (33). While the cumulative dosage and duration of treatment were the main predictors of ototoxicity, the peak serum concentrations measured were not significantly related to hearing loss. The authors state that the reasons for the lack of association is unclear, but reported wide variability in peak concentrations even when patients received the same dosage. Studies in India, a high burden country for MDR TB, drug susceptible TB and co-infection with HIV and TB (HIV/TB), have shown low incidence of hearing loss among patients receiving treatment regimens containing aminoglycosides (9,10,25). Among a cohort of 58 persons living with HIV/MDR TB treated with capreomycin, 9% (n=5) developed hearing loss (10). A study among 38 MDR TB patients without HIV infection treated with kanamycin identified only one case of hearing loss (3%) (9). There were five patients that required a decrease of administration from daily to 3 days a week, who may have developed hearing loss had they stayed at the higher dosage. The definition of hearing loss was not provided in the publications for either of these studies. Long-term audiologic monitoring of a cohort of 64 patients with MDR TB in India identified an overall incidence of ototoxicity of 19%; incidence by drug was 21%, 15% and 25% for amikacin, kanamycin, and capreomycin, respectively (25). Ototoxicity was defined as high frequency loss based on the common definition with PTA, as a change of 20 dB at any one frequency or 10 dB at consecutive frequencies. This study had a small sample size in each drug group, which may have biased the results. A study in Bangladesh, a high burden country for drug susceptible and MDR TB, found an incidence of ototoxicity of 4.4% among 427 MDR patients treated with kanamycin (40). Patients were given initial daily doses of kanamycin at 500 mg for weight <33 kg, 750 mg for weight 33 – 50 kg and 1,000 mg for weight >50 kg. The dosage was later adjusted to 15 mg/kg 3 times a week to reduce adverse events. This reduced dosage may be responsible for the lower incidence of ototoxicity reported. The lower incidence may also be due to the method of ototoxicity measurement, but it is unclear from the article.

In low TB burden, high income countries the reported incidence of ototoxicity among persons treated with aminoglycosides for TB is typically higher than is observed in higher TB

burden/lower income countries, above 40% (24,41,42). A cohort study of 100 MDR TB patients in the United Kingdom given either amikacin or capreomycin at 15 mg/kg found an incidence of ototoxicity of 59% (24). Ototoxicity was found to occur among amikacin users at 5.8 times the rate among capreomycin users, consistent with the literature that capreomycin is the less ototoxic drug. This study also found an improvement of hearing loss after treatment was stopped in one patient, with ototoxicity and improvement confirmed by PTA. A case review of MDR TB patients treated at the Saint-Pierre University Hospital in Brussels found that 50% had developed ototoxicity approximately 2 months following treatment initiation with amikacin (41). In a study of the National TB Surveillance System in the United States, 13% of the sampled MDR TB patients experienced hearing loss (8). The study included all XDR TB cases, a 75% simple random sample of MDR TB cases from California and New York City, and a 50% simple random sample from Texas. While all patients received an aminoglycoside, the specific aminoglycosides given to this population is not clear and the association between aminoglycosides and ototoxicity was not studied. The other studies performed in the US have estimated a similar incidence of ototoxicity (2.8% - 16.7%) (43–46).

Risk Factors for Ototoxicity

Cumulative dosage of aminoglycosides is considered to be the main risk factor for ototoxicity, as ototoxicity results from accumulation of aminoglycosides in the cochlea. Several other risk factors for ototoxicity that have been identified are HIV infection, older age, creatinine increase and exposure to high levels of noise (17). However, there is inconsistencies in the significance of the factors association with ototoxicity. In the United Kingdom, use of amikacin, age and creatine increase were significantly associated with hearing loss in a retrospective cohort of 50 MDR TB cases ($p = 0.02$, $p = 0.02$, $p = 0.01$) (26). Fifty-eight percent of patients received amikacin, 22% received capreomycin and 8% received streptomycin, although some switching of regimens occurred. 28% of all patients developed ototoxicity. Race, gender, HIV status, duration and dosage of the aminoglycoside were also considered as risk factors but were not found to be

significant. Studies in Australia and Iran however found no significant association between age and ototoxicity (31,47). The Australian study included patients treated for non-Tuberculosis Mycobacterium (NTM) with IV amikacin. The researchers also found no association for creatinine levels or dosage. They did find an inverse relationship between duration of treatment and ototoxicity, that they hypothesize exists because patients with early signs of hearing loss had early termination of treatment (31). The study in Iran only reported risk factors for any adverse effects, so it is not possible to say which is linked specifically to ototoxicity. However, none were found to be significant expect for comorbidities for TB (47). No other studies have been found that have examined risk factors for aminoglycoside-induced ototoxicity in TB patients. It is important to recognize the variability in the measurement of ototoxicity across studies. Hearing loss based on self-report is likely to underestimate ototoxicity, since measures of ototoxicity by audiograms are more sensitive and can classify loss at higher frequencies than those used in everyday speech and hearing. Further, the setting in which persons are exposed to treatment with aminoglycosides or other factors that may cause hearing loss may also impact estimates.

There is some growing evidence that some persons have a genetic predisposition for aminoglycoside ototoxicity. Mutations in multiple genes that affect the mitochondria are thought to be responsible for the susceptibility. The main mutation, A1555G, has been found in up to 33% of patients experiencing aminoglycoside-induced ototoxicity (21). A study of newborns in Texas estimated that the carriage rate of the A1555G mutation is 0.09%, which corresponds to hundreds of thousands of people in the US. The mutation has been found in a wide variety of ethnic groups as well. Studies have suggested that even one dose of aminoglycosides is sufficient, though not necessary, to cause hearing loss in the genetically susceptible (48). Three cases of ototoxicity reported among children 5 years and younger receiving treatment for septic episodes during leukemia treatment were all shown to carry the A155G mutation (49).

JUSTIFICATION FOR STUDY

The association between aminoglycoside use and ototoxicity has been well recognized since their introduction but has not been robustly evaluated in patients with MDR TB. It is commonly reported as an adverse event in MDR TB studies, but few have directly studied the association. Since hearing loss is most commonly reported as a secondary outcome, it is difficult to attribute the risk in many studies to which, if any, aminoglycoside is responsible for the ototoxicity. Also there are no standardized mechanisms for systematically documenting adverse events in TB treatment, so the documentation and definition of hearing loss can vary. There are a limited number of studies that have directly evaluated aminoglycoside toxicity among TB patients, and the incidence of ototoxicity has ranged from 0-60% (Table 2). There is a general trend of a higher incidence in high burden, low income countries compared to low burden, high income countries, but it does not hold for all studies.

While there are promising new drugs for MDR TB in research and development, aminoglycosides remain a key component of treatment for the estimated 601,000 cases of MDR TB worldwide (5). The current evaluation aims to address this gap in knowledge by characterizing ototoxicity, estimating the frequency of ototoxicity, and estimating the association between sociodemographic and clinical factors and ototoxicity risk among a cohort of drug-susceptible and MDR TB patients in the United States from 1985-2013.

OBJECTIVES

The specific aims of this evaluation are to:

1. Describe the overall study sample of hospitalized TB patients in from 1985-2013
2. Describe the use of aminoglycosides for TB treatment in the study sample
3. Describe the incidence of ototoxicity in the study sample
4. Determine the association between aminoglycosides and ototoxicity, overall and by type of aminoglycoside

METHODS

DATA SOURCE

The data for this study were initially collected in two separate studies. The first involved medical chart review of patients admitted to the Tuberculosis Unit of the University of Texas Health Science Center (UTHSCT) in Tyler, Texas between 1985 and 2010 (50). During this period, approximately 3000 patients were admitted to the hospital. All patients who had: a) drug-resistant tuberculosis, 2) HIV infection, or 3) therapeutic drug monitoring were included in the original study population. In addition, a 25% simple random sample of the other, uncomplicated tuberculosis cases were also added. The second study was conducted at Texas Center for Infectious Diseases (TCID) and A.G. Holley Hospital (AGHH) in Lantana, Florida (51). Medical record abstraction was carried out for patients admitted to both centers between 1988 and 2015. One hundred percent of patients who had therapeutic drug monitoring were included in the study. The data collected from all three study sites was combined into a single dataset for all patients who received therapeutic drug monitoring. The combined sample contains 397 admissions and 356 patients.

The two parent studies were reviewed and approved by the Institutional Review Boards (IRB) at the study sites and at the Centers for Disease Control and Prevention. The protocol for the current secondary analysis using de-identified data was reviewed by the Emory University IRB and considered exempt from human subjects research approval.

STUDY POPULATION

The original data were provided in multiple related tables and was cleaned and merged before analysis was completed. The dataset was restricted to patients with at least two audiograms following their admission to one of the study sites (n = 81). The dataset was formatted to have one observation for each audiogram for each patient in order to conduct longitudinal analysis. In

the case of multiple admissions of the same patient, hospital admission data, including drug regimen and comorbidities, were associated with the audiogram(s) that occurred within that admission period. The multiple admissions were then treated as a single subject or cluster.

OUTCOME: OTOTOXICITY

The outcome of interest for this subsample is ototoxicity defined as a change from baseline in an audiogram of at least 20 dB at any one frequency or 10 db at two adjacent frequencies if a baseline audiogram existed. This is the commonly accepted definition of ototoxicity in the literature (23,25,26,31). The initial audiogram was considered to be the baseline measurement if it occurred within 3 months of admission. If no baseline fit these criteria, ototoxicity was defined an audiogram at 4 months after start of aminoglycoside treatment or later and at least one frequency greater than 40 db. In standard PTA the frequencies tested are 250, 500, 1000, 2000, 4000 and 8000 Hz. They can be extended up to 9,000, 10,500, 11,200, 12,500, 14,000 and 16,000 Hz. The audiograms for this study were reported as the maximum decibel value for three ranges of frequencies: less than 500 Hz, 500-2,000 Hz and greater than 2,000 Hz. The < 500 Hz and 500-2,000 Hz categories are considered adjacent frequencies and the 500-2,00 Hz and > 2,000 Hz categories are considered adjacent frequencies. If a patient had more than one measurement in a 2-week interval only the first observation from that period was kept.

EXPOSURE: AMINOGLYCOSIDES

The exposure of interest, aminoglycosides, was investigated in multiple ways. Initially, aminoglycoside use was defined as any dosage of amikacin, capreomycin, streptomycin or kanamycin during the current hospitalization. Patients who received no aminoglycosides served as the reference group. The majority of patients changed the aminoglycoside prescribed during their admission. Only aminoglycosides started prior to a given audiogram measure were considered as exposures. The exposure was also evaluated as cumulative dosage of any aminoglycoside and total duration of aminoglycoside treatment measured in days. The total duration was calculated by adding the duration in days given in the original dataset for each

aminoglycoside that was started prior to the audiogram. It was treated as a continuous variable and a categorical variable: < 47 days (Reference), 47-435 days and >435 days. The cumulative dosage of all aminoglycosides was calculated from the daily dosage, frequency of delivery and duration in days given for each instance of aminoglycoside treatment. If the aminoglycoside was given for an even number of weeks, the cumulative dosage was calculated through multiplication of the dosage, frequency and duration (ex: 650 mg*5 days/week*4 weeks). For instances where the duration of aminoglycoside treatment was not an even number of weeks, for example 4 weeks and 3 days, the cumulative dosage was determined off of a systematic delivery schedule. All aminoglycoside delivery frequencies were assumed to start on a Monday so that a 5 day/week delivery schedule would be Monday-Friday and a 3 day/week delivery schedule would be Monday, Wednesday, Friday. This scheduling was used to calculate total cumulative dosage of aminoglycosides, assuming all aminoglycosides were initiated on a Monday. For example, if the duration of aminoglycoside treatment was 4 weeks and 3 days, a patient with a delivery frequency of 5 days/week would be considered to have received 3 doses for the extra 3 days. A patient with a delivery frequency of 3 days/week would be considered to have received 2 doses for the extra 3 days.

Other Sociodemographic and Clinical Characteristics

Smoking and history of TB were each recoded into categorical variables based on multiple binary variables. History of aminoglycoside use (for indications prior to the current TB episode) was evaluated from a treatment history table and defined as any exposure to streptomycin, amikacin, kanamycin, and/or capreomycin. Amikacin and kanamycin exposure were combined into one variable expressing exposure to either drug as they are often treated interchangeably in MDR TB regimens and very few patients received kanamycin in the study population. Route of delivery was recoded if the value was recorded as oral or tube as aminoglycosides are not available for delivery this way; they are only provided intramuscularly (IM) or intravenously (IV). The variable was assigned to the previous instance of aminoglycoside treatment as patients with these

errors had the same delivery route for all other instances. Frequency of drug delivery was re-categorized into a smaller number of categories (5-7 times/week, 2-3 times/week, 1 time/week) to increase cell size of some small cells and improve later analysis.

DESCRIPTIVE ANALYSIS

All analyses were conducted using Statistical Analysis Software 9.4 (SAS). Descriptive analysis of the study population was carried out for demographic characteristics and covariates of interest (age, gender, race, dosage, TB history, comorbidities, etc.) The descriptive characteristics were calculated for the entire study population and stratified by the UTHSCT and TCID/AGHH study sites. A chi-square test of independence was conducted for the two sites to determine if the distribution was significantly different. The frequency and percentage of each dichotomous or categorical covariate was calculated using PROC FREQ in SAS. A Fisher's Exact Test was used if the expected cell frequencies were less than 5. The continuous variables were described using the appropriate measures of central tendency and spread. An ANOVA F test was carried out for continuous variables if the mean was the appropriate measure to determine if the two study sites had significantly different distributions of the demographics. A median test, or Brown-Mood test, was carried out for continuous variables if the median was the appropriate measure. The rate of ototoxicity over time was examined by week and by month from admission. A survival curve was also generated for the overall population and stratified by the dichotomous and categorical aminoglycoside variables. A Log-Rank test was used to determine if the curves were statistically different.

BIVARIATE ANALYSIS

A crude odds ratio (OR) and 95% confidence interval (CI) was calculated as the measure of association between each metric of the exposure of interest, sociodemographic or clinical characteristic and the outcome through simple logistic regression. Wald tests were used to determine the significance of the ORs with a cutoff of $p = 0.05$ as significant. For continuous

variables, the association was examined for a continuous and categorical version of each variable. Some categorical variables were collapsed from the descriptive analysis due to small numbers in strata. A stratified analysis of the bivariate associations was also carried out to examine possible interaction by study site (UTHSCT or TCID/AGHH). Zero cell issues that were encountered during stratification were compensated for by calculating exact estimates.

MULTIVARIATE ANALYSIS

Multivariate logistic regression was performed using the overall sample to assess the association between the exposure and outcome controlling for potential effect measure modifiers and confounders identified in the bivariate analysis and the literature. If the bivariate association between a continuous variable and ototoxicity was statistically significant for at least one sample or at least one level of categorical variable was statistically significant it was examined as a potential covariate (<0.10). If it was not significant in the bivariate analysis but identified as significant in the literature it was also included as a potential covariate. Generalized estimating equations (GEE) were used to account for the correlated and longitudinal nature of the data as each patient had at least two measurements of the outcome over time. Each patient was treated as a cluster, including all admissions to the treatment center. The log-odds of ototoxicity were plotted over time to determine an appropriate time variable in the model. Based off of these graphs, time was included in the model as 2-week intervals from admission. The appropriate working correlation structure was determined using a crude model with only the exposure and time: unstructured, auto-regressive (AR(1)), and Toeplitz working correlation structures were tested. The model was run with each correlation structure and the appropriate structure was chosen by comparing the Quasi-likelihood under the Independence model Criterion (QIC), standard errors and expected correlations in the data to be the appropriate structure. Toeplitz was chosen to be the most appropriate based on these criteria.

The initial multivariate model included the exposure of interest (cumulative dosage or total duration), time, age and gender. Forward selection was then performed manually for the remaining covariates of interest identified in the bivariate analysis and literature review. Each covariate was individually added to a model including the exposure, time, age and gender. The covariate with the lowest Wald p-value fitting the selection criteria ($p \geq 0.25$) was added into the model. The process was repeated until no covariates met the selection criteria. Collinearity assessment was carried out for the saturated model that was found to converge. Then the significance of the potential effect modifiers were determined using Score Tests for the interaction terms. Any interaction terms that were not significant were dropped from the model ($p > 0.05$). After interaction assessment, confounding was assessed by estimating the change in effect for the addition of each potential confounders. An estimate outside 10% of the full model was considered to be a confounder and included in the final model. The final model was used to calculate an odds ratio (OR) and 95% confidence interval (CI) for the independent association between aminoglycoside use and ototoxicity. QIC, a goodness of fit statistic, was used to select the final model.

RESULTS

DESCRIPTIVE ANALYSIS

A total of 81 patients had at least 2 audiograms during their admission for TB disease and were included in the analytic sample; 33 patients were from the UTHSCT site and 48 patients from the TCID/AGHH sites for the second study. The average age of patients at admission was 43 years (standard deviation (SD) 7.0); 44 and 42 years at UTHSCT and TCID/AGHH, respectively (Table 3). The majority of patients were male (72.8%; n = 59), with a slightly lower proportion of males in the UTHSCT site (75.8%) compared to the TCID/AGHH (70.8%) sites. The largest racial and ethnic group in the overall sample was Hispanic (n = 36) followed by White (n=18), Black (n=13) and Other (n=13). In the overall sample 49 (62.8%) of the patients were born outside the United States (non-US); there was a significant difference in the proportion of non-US born between sites, with 15 non-US born patients (48.4%) from UTHSCT and 34 non-US born patients (72.3%) from TCID/AGHH ($\chi^2 = 4.59$, $p = 0.03$).

Just over half (51.6%; n = 42) of all patients had a history of TB disease, defined as recurrent, relapsed or evidence based on chest x-ray of prior TB disease without a previous TB diagnosis. History of TB was dependent on the study site ($\chi^2 = 7.65$ $p = 0.01$), with 33.3% (n = 111) of patients at UTHSCT and 64.6% (n = 31) of patients at TCID/AGHH reporting a TB diagnosis prior to the current TB episode. Only a quarter of patients had a history of aminoglycoside exposure (n = 17, 25.3%). Previous aminoglycoside treatment did not significantly differ between study sites, as it was seen in 26.9% of patients at UTHSCT and 22.7% at TCID/AGHH ($\chi^2 = 0.16$, $p = 0.69$).

Overall, 7 (8.64%) patients were HIV positive and 3 (3.7%) patients had unknown HIV status. The proportion of patients with HIV infection was slightly, but not significantly, higher among patients at TCID/AGHH ($\chi^2 = 0.08$, $p = 0.57$): 6.1% vs at UTHSCT and 10.4% at TCID/AGHH.

Eighteen (n=18; 22.8%) patients had diabetes mellitus overall, a common comorbidity for TB (6 (9.4%) patients at UTHSCT and 12 (25.0%) patients at TCID/AGHH). Alcohol use, defined as current or former alcoholism, was significantly higher among patients at TCID/AGHH ($\chi^2 = 6.80$, $p = 0.001$). Multi-drug or rifampin resistant (RR) TB was identified in 62 (76.5%) patients in the overall sample and 25 (75.8%) patients at UTHSCT and 37 (77.1%) patients at TCID/AGHH.

AMINOGLYCOSIDE EXPOSURE

The initial exposure of interest, treatment with any aminoglycosides, was administered to the majority (n=71; 87.7%) of patients in the overall sample. Thirty-two (97.0%) and 39 (81.3%) patients at UTHSCT and TCID/AGHH, respectively, had treatment with any aminoglycoside. Use of aminoglycosides was significantly greater among patients at the UTHSCT site ($p = 0.04$, Fisher's exact test). In the overall sample, 54 (66.7%) patients were given amikacin, 3 (3.7%) patients were given kanamycin, 29 (35.8%) were capreomycin, and 17 (21.0%) patients were given streptomycin. At UTHSCT, 20 (60.0%) patients were given amikacin, 2 (6.1%) were given kanamycin, 23 (69.7%) were given capreomycin and 12 (36.4%) were given streptomycin. At TCID/AGHH 34 (70.8%) patients were given amikacin, 1 (2.1%) was given kanamycin, 6 (12.5%) were given capreomycin and 5 (10.4%) were given streptomycin. Capreomycin was given to a significantly higher proportion of patients at UTHSCT compared to TCID/AGHH ($\chi^2 = 27.83$ $p = <0.0001$). Streptomycin was also given to a significantly higher proportion of patients at UTHSCT ($\chi^2 = 7.94$ $p = 0.01$). There is overlap in the number of patients who received each aminoglycoside as 22 (21.2%) patients received two aminoglycosides and 5 (6.2%) received three aminoglycosides during their treatment in the overall sample. Among patients who had 2 or more aminoglycosides, only one patient did not have amikacin as part of their regimen. The total number of aminoglycosides received was dependent on the study site ($p < 0.001$, Fisher's exact test). The aminoglycoside patients were receiving changed up to 9 times within a patient's admission. In the overall sample, 6 (7.4%) patients had 1 change, 7 (8.6%) had 2 changes, 6 (7.4%) had 3 changes and 6 (7.4%) had 4 or more changes. The number of changes was

dependent on study site (p = 0.01, Fisher's exact test). At UTHSCT, 4 (12.1%) patients had 1 change, 4 (12.1%) had 2 changes, 5 (15.2%) had 3 changes and 4 (12.1%) had 4 or more changes. At TCID/AGHH 2 (4.2%) patients had 1 change, 3 (6.3%) had 2 changes, 1 (2.1%) had 3 changes and 2 (4.2%) had 4 or more changes.

Patients were given aminoglycosides for an average of 133 days (standard deviation (SD)=404.0). The average duration was significantly longer for patients at UTHSCT, who had an average of 438 days (SD= 684.5) compared to 87 days (SD=135.0) for patients at TCID/AGHH (F=12.33; p=0.001). The median cumulative dosage of any aminoglycosides for the overall sample was 48,000 milligrams (mg) (interquartile range (IQR) 21,000-167,000 mg). The median cumulative dosage of any aminoglycoside was 147,500 mg (IQR 39,000-254,875 mg) at UTHSCT and 38,875 mg (IQR 14,025-67,000 mg) at TCID/AGHH. The difference in cumulative dosage was statistically higher at UTHSCT ($\chi^2 = 24.00$, p = 0.0003). The median daily dosage of any aminoglycoside was 600 mg (IQR 500-750 mg). The distribution of median daily dosage was dependent on the site and was significantly greater at TCID/AGHH (700 mg, IQR 425-750 mg) compared to UTHSCT (550 mg, IQR 500-765 mg) ($\chi^2 = 97.38$, p = 0.0003). The frequency of delivery of aminoglycosides was significantly more frequent at TCID/AGHH, where 56.7% (n = 76) of aminoglycosides were delivered 5-7 days/week (p <0.001, Fisher's Exact Test). At UTHSCT, only 9.7% of aminoglycosides were delivered 5-7 days/week and 90.3% (n = 102) of aminoglycosides were delivered 2-3 times/week. In the overall sample, the aminoglycoside was delivered intramuscularly 151 (43.1%) times and intravenously 199 (56.9%) times. The distribution of delivery route was significantly different between study sites ($\chi^2 = 4.00$, p = 0.05). Aminoglycosides were delivered more frequently intravenously at UTHSCHT (61.8%) compared to TCID/AGHH (51.2%).

OTOTOXICITY

Ototoxicity was defined as a change in an audiogram of at least 20 dB at any one frequency, 10 dB at two adjacent frequencies (<500 Hz and 500-2,000 Hz or 500-2,000 Hz and >2,000 Hz) or an audiogram 4 months or greater from start of aminoglycoside treatment with at least one frequency greater than 40 dB if no baseline (≤3 months from hospital admission) existed. Ototoxicity was detected in 27 (33.3%) patients. Ototoxicity was significantly higher among patients at the UTHSCT study site (n=19; 57.6%) than patients at the TCID/AGHH study sites (n=8; 16.7%) ($\chi^2 = 14.73$, p=0.0001). In the overall sample 5 (6.2%) patients had ototoxicity in only one ear, or unilateral toxicity; 3 (9.1%) were at UTHSCT and 2 (4.2%) were at TCID/AGHH. The remaining patients with ototoxicity had hearing loss in both ears, or bilateral toxicity. The difference in the location of ototoxicity between sites was statistically significant (p = 0.0003, Fisher's Exact Test).

When considering weeks from hospital admission, the rate of ototoxicity was highest in week 5 for the overall sample and at TCID/AGHH (10.1 cases per 1,000 person-weeks and 12.7 cases per 1,000-person weeks) (Figure 1a). For the patients in UTHSCT site the highest rate occurred in week 4 (7.6 cases per 1,000-person weeks). The rate of ototoxicity among patients at UTHSCT is generally higher than the overall sample and TCID/AGHH for the remaining weeks of the study period. UTHSCT also experienced cases up to 57 weeks from admission. When considering months from admission, the highest rate of ototoxicity for the overall sample and patients at TCID/AGHH occurred in month 2 (34.0 cases per 1,000 patient-months and 46.5 cases per 1,000 patient-months) (Figure 1b). The highest rate of ototoxicity at UTHSCT occurred in month 5 (58.8 cases per 1,000 patient-months). The increased rate among UTHSCT patients in month 5 corresponds the increased rate by patient-weeks seen around week 20 in Figure 1a. The last cases of ototoxicity occurred 15 months from admission.

The survival curves of weeks to toxicity appears to differ between patients with and without aminoglycoside exposure after 20 weeks from admission (Figure 2a). However, these curves are not statistically significant ($\chi^2 = 1.55$, p =0.21). When plotting the survival probability by study site, the rate of ototoxicity among patients at UTHSCT was significantly higher than patients at TCID/AGHH ($\chi^2 = 8.33$, p =0.003).

OTHER ADVERSE EVENTS AND TB TREATMENT OUTCOME

Other adverse events were experienced by 9 (11.1%), 7 (21.2%) and 2 (4.2%) patients in the overall sample, and at UTHSCT and TCID/AGHH respectively. These included night sweats, gastrointestinal issues, thrombocytopenia, hypothyroidism, loss of taste and vision loss. The overall adverse events experienced were significantly different between study sites (p = 0.02, Fisher's Exact Test). In the overall sample, 26 (32.1%) patients were cured, another 6 (7.4%) completed treatment, 12 (14.8%) failed treatment, 3 (3.7%) died, 3 (3.7%) were lost to follow up, and 31 (38.3%) did not have an outcome available at the time of data collection. Of those without a treatment outcome, 1 (3.2%) was missing treatment outcome and 30 (96.8%) were still on treatment following discharge from the hospital. At UTHSCT, 10 (30.3%) patients were cured, 6 (18.2%) completed treatment, 11 (33.3%) failed treatment, 3 (9.09%) died and 1 (3.0%) was lost to follow up, and 2 (6.1%) did not have a treatment outcome available. In patients at the TCID/AGHH sites, 16 (33.3%) were cured, 1 (2.1%) failed treatment, 2 (4.2%) were lost to follow up and 29 (60.4%) were continuing treatment after hospital discharge. The treatment outcomes were significantly different between sites (p <0.001).

BIVARIATE ANALYSIS

Because differences were noted in the distribution of patient characteristics between sites for several variables in the initial descriptive analysis, we examined all bivariate associations between characteristics and ototoxicity overall and by study site strata (UTHSCT and TCID/AGHH). Age as a continuous variable was not significantly associated with ototoxicity

overall or by study site (all 3 ORs 1.01; Table 4). There was a significantly higher odds of being male among patients who experienced ototoxicity overall (OR=2.87, 95% CI 0.86, 9.58; p=0.04) and at the TCID/AGHH sites (OR=5.56, 95% CI 1.02, infinite; p=0.05), but the association was not significant in patients at UTHSCT (OR=1.48, 95% CI 0.22, 10.06; p=0.92). The odds ratio for gender at TCID/AGHH is a median unbiased estimate, as the conditional distribution could not be maximized. Therefore the estimate is unreliable but does signify that gender may be associated with ototoxicity. Race/ethnicity, categorized as White, Black, Hispanic or other, was not significantly associated with ototoxicity overall, or at the UTHSCT or TCID/AGHH sites. Place of birth, US born compared to non-US born, was close to significance overall and among patients at the TCID/AGHH sites (OR = 0.40, 95% CI 0.15, 1.06, p = 0.07, OR = 0.22, 95% CI 0.04, 1.16, p = 0.07). The association in the UTHSCT site was far from statistically significant (p = 0.83). History of TB was significantly associated with a significantly lower odds of ototoxicity overall (OR=0.25, 95% CI 0.09, 0.67; p=0.01), but not in the individual site strata (UTHSCT OR=0.27, 95% CI 0.06, 1.22; p=0.09 and TCID/AGHH OR=0.48, 95% CI 0.10, 2.24 p=0.35). Drug resistance was not significantly associated with ototoxicity in the overall (p=0.07) or TCID/AGHH sample (p=0.88), but it was significantly associated in the UTHSCT sample (p = 0.01). Among the UTHSCT patients, MDR or RR TB was 18 times more likely among patients with ototoxicity (OR = 18.00, 95% CI 1.86, 174.21; p=0.01). None of the remaining demographic covariates are significantly associated with ototoxicity in bivariate analysis.

AMINOGLYCOSIDE EXPOSURE

In a bivariate logistic regression analysis, the odds of any aminoglycoside exposure in the current treatment episode was not statistically significant (p = 0.35) (Table 4). Kanamycin exposure 8.21 times more likely among patients with ototoxicity compared to patients without ototoxicity (95% CI 1.22, infinite; p = 0.03). This estimate is a median unbiased estimate from exact regression as only 3 patients received kanamycin. KM was not significantly associated with ototoxicity after stratification (p = 0.32, p = 0.17). The odds of capreomycin exposure was 4.59 times higher

among patients with ototoxicity (95% CI 1.71, 12.34; p = 0.003). After stratification it was no longer significantly associated with ototoxicity (p = 0.08, p = 0.31). Amikacin and streptomycin exposure were not significantly associated in the overall sample or stratified by site. When considering the total number of aminoglycosides a patient received during their current treatment episode, ototoxicity was significantly higher among patients who received 2-3 aminoglycosides compared to patients who received no aminoglycosides (OR = 5.82; 95% CI 1.03, 32.79; p = 0.002).

Total duration of aminoglycoside treatment measured in days was also considered as a potential main exposure. In the bivariate analysis, the continuous duration had a significant null association with ototoxicity in the overall sample and UTHSCT patients (OR = 1.00, 95% CI 1.00, 1.01, p <0.001; OR = 1.00, 95% CI 1.00, 1.01, p = 0.01). The null association was not statistically significant in the TCID/AGHH sample (OR = 1.00, 95% CI 1.00, 1.01, p = 0.20). Total duration of aminoglycoside treatment was treated as a categorical variable (<47 days, 47-435 days, >435 days). In the overall sample, the odds of ototoxicity was 1.67 times higher among patients with a total duration of greater than 435 days compared to patients who had <47 days of aminoglycoside treatment (95% CI 2.10,53.33,p < 0.0001). There was no meaningful increased odds of ototoxicity among patients with 47-435 days of treatment compared to patients with < 47 days of treatment (OR = 0.97, 95% CI 0.25, 3.71, p = 0.02). At the UTHSCT site, the odds of ototoxicity was 9.75 times higher among patients with greater than 435 days of aminoglycoside treatment (95% CI 0.95, 99.96, p = 0.01). While statistically significant, the confidence interval is very wide, so the magnitude of the association is not reliable. The association was not statistically significant among patients at TCID/AGHH (p = 0.42 for duration 47-435 days, p = 0.16 for duration > 435 days).

In the overall sample, the continuous cumulative dosage also had a significant null association with ototoxicity (OR = 1.00, 95% CI 1.00, 1.00; p=0.0001); the association was similar when

examined by site. Since cumulative dosage as a continuous variable was not readily interpreted to a clinical application (per mg increase in dose), cumulative dosage was also categorized by the quartiles among patients who received aminoglycosides; patients who were not treated with aminoglycosides served as the reference group. The odds of a cumulative dosage greater than 181,375 mg was 13.00 times higher among patients with ototoxicity compared to patients without ototoxicity (95% CI 1.92, 87.99; p=0.01). After stratification, the association was no longer significant. In the overall sample, the association was not significant for patients with a cumulative dosage < 32,000 mg and 32,000-181,375 mg (p = 0.29, p = 0.54). While not significant, the magnitude of the association (OR) between patients with a cumulative dosage < 32,000 mg and patients who received no aminoglycosides was less than 1.00, suggesting a protective effect. However, only 1 patient developed ototoxicity in this dosage category. There was no significant association between cumulative dosage of aminoglycosides and ototoxicity when examined independently by study site.

Other adverse Events and TB Treatment Outcome

Other adverse events were 9 times more likely among patients with ototoxicity compared to patients without ototoxicity in the overall sample (OR = 9.10, 95% CI 1.74, 47.57; p=0.01). There was no significant association between other adverse events and ototoxicity in the individual site stratified analyses (OR=6.00, 95% CI 0.63, 57.02; p=0.12 for UTHSCT and OR =5.57, 95% CI 0.31, 99.88; p=0.24 for TCID/AGHH). Compared to patients who had an indeterminate outcome on discharge, patients who were reported as cured experienced a 3.57 times increase in the odds of ototoxicity (OR = 0.28, 95% CI 0.08, 0.95, p = 0.002). The association was not significant after stratification by site (p = 0.87, p =0.52).

MULTIVARIATE ANALYSIS

Since previous research and our bivariate analysis suggest an increased risk for ototoxicity with increasing cumulative dosage, and cumulative dosage and risk of ototoxicity are both likely to increase with increased time in the hospital, we considered time from admission as a potential

confounder in the multivariate model. To determine how time should be included in the model, the log-odds of ototoxicity in the overall sample was plotted against time from admission both in weeks and in months as this is the measure that logistic regression requires to be linear (Figure 3a-3b). Based on visual inspection of the plot of log-odds over weeks, time from admission defined in two-week intervals was also tested The log-odds over time in both two-week intervals and months followed similar time trends (Figure 3c). PROC GENMOD in SAS requires only one observation in each time for longitudinal analysis and measuring time in months required a greater number of observations deleted to fit this criterion. Therefore, time from admission in two-weeks intervals was chosen to be the more appropriate measure and was included as a continuous term in the multivariate models.

Longitudinal logistic regression requires defining a working correlation structure to model the variances between the measures within clusters, which are the patients in this sample. Unstructured, autoregressive and Toeplitz working correlation structures were tested due to the longitudinal nature of the data and evenly spaced measures as time was measured in two-week intervals. Toeplitz was chosen as the proper working structure as it the only correlation structure that could converge. After choosing the appropriate measure of time and working correlation structure we conducted a longitudinal logistic regression using cumulative dosage and total duration of aminoglycosides as the main exposure variables.

EXPOSURE: CUMULATIVE DOSAGE OF AMINOGLYCOSIDES

Cumulative dosage was initially treated as a categorical variable for the multivariate analysis. The lower two categories were collapsed together, so patients with a dosage of zero were included with patients with less than 32,000 mg. Therefore, the cumulative dosage of aminoglycoside categories for the multivariate analysis were: 0-31,999 mg (reference), 32,000-131,785, and >131,785. A full multivariate model for was determined through forward selection on an initial model containing cumulative dosage, time from admission, age and gender. Variables were only

included if their p-value was ≤ 0.25 after addition into the initial model. Place of birth was initially added to the model as it had the lowest Wald p-value. Adverse events was then added to the model as it had the lowest Wald p-value for a model containing cumulative dosage, gender, age, time, and place of birth (equation 1). None of the remaining covariates were significant when added into a model containing cumulative dosage, gender, age, time, place of birth, and other adverse events. A stratified analysis was attempted as it was significant in the bivariate analysis, however the models would not converge when stratified due to the small number of ototoxicity cases in site 2. Therefore, the analysis was only carried out for the overall sample.

$$Logit(Ototoxicity_{ij}) = \beta_0 + \beta_1 Cumulative\ Dosage_{ij} + \beta_2 Time_{ij} + \beta_3 age_{ij} +$$

$$\beta_4 gender_{ij} + \beta_5 Place\ of\ Birth_{ij} + \beta_6 Other\ Adverse\ Events_{ij} \quad (Eq. 1)$$

In this multivariate regression, only the cumulative dosage >181,375 mg compared to a dosage <32,000 mg was statistically significant (OR = 8.46, 95% CI 1.00, 71.24, p = 0.05). Therefore, cumulative dosage was also considered as a dichotomous variable; patients with greater than 131,785 mg compared to patients with less than 131,785 mg. Forward selection was repeated with the same process and history of TB was the first covariate to be added in. It was not significant when the cumulative dosage was a three-level variable but was significant for the dichotomous exposure. Other adverse events was the next variable added to the model containing cumulative dosage, time, age, gender and history of TB. Place of birth was no longer significant after dichotomizing cumulative dosage and was not included in the model. The full model for dichotomous cumulative dosage is seen below (equation 2).

$$Logit(Ototoxicity_{ij}) = \beta_0 + \beta_1 Cumulative\ Dosage_{ij} + \beta_2 Time_{ij} + \beta_3 age_{ij} +$$

$$\beta_4 gender_{ij} + \beta_5 History\ of\ TB_{ij} + \beta_6 Other\ Adverse\ Events_{ij} \quad (Eq. 2)$$

An interaction assessment revealed no significant interaction between cumulative dosage and age, gender, history of TB or other adverse events. Confounding assessment was done for all possible subsets of confounders by removing other adverse events individually and history of TB and adverse events together, as adverse events is not significant without history of TB. Removing only other adverse events did not show confounding as the OR was within 10% of the OR for the full model. Removing both did show confounding as the OR was outside 10% of the full model (full OR = 3.41, reduced OR = 4.14). To choose the final model the QIC was compared for the full model in equation 2 and the reduced model in equation 3:

$$Logit\left(Ototoxicity_{ij}\right) = \beta_0 + \beta_1 Cumulative\ Dosage_{ij} + \beta_2 Time_{ij} + \beta_3 age_{ij} +$$

$$\beta_4 gender_{ij} + \beta_5 History\ of\ TB_{ij} \quad (Eq. 3)$$

The reduced model has a lower QIC (231.38) compared to the full model (QIC = 241.40), so it is considered the more appropriate model. A collinearity assessment was performed for the final model (eq. 3) and no variables were found to be collinear. Controlling for time from hospital admission, age, gender and history of TB, the odds of ototoxicity is 3.75 times higher among patients with a cumulative dosage greater than 131,785 mg compared to patients with a cumulative dosage less than or equal to 131,785 mg (95% CI 1.42,9.96; p = 0.01). The estimates and odds ratios for the covariates can be seen in Table 5.

Exposure: Total Duration

Total duration of aminoglycoside treatment was also considered as a potential exposure. It was treated as a continuous variable measured in days. The same covariates were added to the model as for cumulative dosage as an exposure. Median dosage of any aminoglycoside was also considered as a potential covariate as it was significant in the stratified bivariate analysis and dosage is otherwise not controlled for. The full model that successfully converged and estimated the variance function is shown below (Equation 4).

$$Logit(Ototoxicity_{ij}) = \beta_0 + \beta_1 Total\ Duration_{ij} + \beta_2 Time_{ij} + \beta_3 age_{ij} +$$

$$\beta_4 gender_{ij} + \beta_5 site_{ij} + \beta_6 History\ of\ TB_{ij} + \beta_7 Drug\ Resistance_{ij}$$

$$+ \beta_8 Other\ Adverse\ Events_{ij} + \beta_9 AMK/KAN_{ij} + \beta_{10} Race_{ij}$$

$$+\beta_{11} Place\ of\ Birth_{ij} + \beta_{12} HIV_{ij} + \beta_{13} IV\ Delivery_{ij} + \beta_{14} IM\ delivery_{ij}$$

$$+\beta_{15} Median\ Dosage_{ij} \qquad (Eq. 4)$$

Interaction assessment revealed none of the interaction terms to be significant. Confounding assessment revealed none of the variables to be confounders as well. All OR's were within 10% of the full model. Backwards selection was then performed in for the full model manually. A variable was removed if the p -value was greater than 0.25, starting with the highest p-value. After selection the final model was defined as shown below in equation 5.

$$Logit(Ototoxicity_{ij}) = \beta_0 + \beta_1 Total\ Duration_{ij} + \beta_2 Time_{ij} + \beta_3 age_{ij} +$$

$$\beta_4 gender_{ij} + \beta_5 site_{ij} + \beta_6 Median\ Dosage_{ij} \qquad (Eq. 5)$$

Age and median dose did have a p-value greater than 0.25, but they were deemed important to the model and were kept in the final model. After adjusting for time, age, gender, site and median dosage, the association between total duration was a significant null association (OR = 1.00, 95% CI: (1.00,1.00), p = 0.03). QIC for the model is 204.67. The estimates for all covariates can be seen in Table 6a.

The total duration was also examined as a categorical variable (< 47 days (reference), 47-435 days, > 435 days) as both levels were statistically significant in the bivariate analysis. However, controlling for time, age and gender the association was no longer statistically significant (p = 0.79 for 47-435 days and p = 0.25 for >435 days). No further model selection was performed for the categorical definition of total duration. Total duration was also dichotomized at 435 days, as

the higher level was significant overall and among patients at the UTHSCT site. Controlling for time, age and gender, the association between a total duration of greater than or equal to 435 days and ototoxicity was significant (p = 0.02) so forward selection was performed with the same criteria as the cumulative dosage model selection. Study site was the first variable added into the model under these criteria (p ≤0.25). None of the remaining covariates were significant when controlling for time from admission, gender, age, and study site. After selection, the full model is shown below in Equation 5:

$$Logit(Ototoxicity_{ij}) = \beta_0 + \beta_1 Total\ Duration_{ij} + \beta_2 Time_{ij} + \beta_3 age_{ij} +$$

$$\beta_4 gender_{ij} + \beta_5 site_{ij} \qquad (Eq. 5)$$

A collinearity assessment was performed for the final model (eq. 5) and no variables were found to be collinear. Controlling for time from admission in two-week intervals, age, gender and study site, the odds of ototoxicity is 2.74 times higher among patients with a total duration of aminoglycoside treatment greater or equal to 435 days (OR = 2.74, 95% CI 1.03,7.34, p = 0.04) (Table 6b).

MODEL FIT

The final model for cumulative dosage (Eq. 3) has a QIC of 231.38. The QICu, which takes into account the number of parameters, for cumulative dosage is 218.20. The final model for total duration (Eq. 5) has a QIC of 226.45 and a QICu of 212.62. As the QIC and QICu model is lower for total duration as exposure, is considered the better fit model. However, cumulative dosage as a predictor of ototoxicity is more clinically relevant. The association for cumulative dosage and ototoxicity was also more statistically significant compared to the association for total duration (p = 0.01, p = 0.04). Therefore, the model containing cumulative dosage as the exposure is considered to be the more appropriate model for the answering the study question.

DISCUSSION

Aminoglycosides remain an important part of MDR TB treatment regimens worldwide. In this study, we report that 33.3% of hospitalized patients treated for TB disease between 1985 and 2015 in the United States with serial audiogram monitoring experienced ototoxicity. The majority of patients (87.7%) were prescribed aminoglycosides during their treatment. Ototoxicity was 3.75 times higher among patients who received a total cumulative dosage of aminoglycosides greater than 131 grams compared to patients who received 131 grams or fewer during treatment, after controlling for age, gender, and history of TB disease (95% CI 1.42, 9.96). We identified a similar relationship between total duration of treatment with aminoglycosides, but cumulative dosage was determined to be a better predictor of ototoxicity (OR = 2.74 95% CI 1.03,7.35, p = 0.04). Cumulative dosage is also a more clinically relevant predictor to monitor during treatment with aminoglycosides. The multivariate analysis suggests that there is a threshold of aminoglycoside exposure above which the risk of ototoxicity increases. Previous studies that have reported an association with cumulative dosage have also presented a dichotomous association; the threshold may biologically represent a threshold of accumulation of aminoglycosides in cochlear cells where cell death is inevitable (23).

The incidence of ototoxicity in this study (33%) was higher than the other studies from the United States who reported a range of ototoxicity from 2.8%-16.7% (43–46). These studies were in only MDR-TB patients who received aminoglycosides at 15 mg/kg 5 days/week**.** The frequency of delivery was higher for the other study population as the majority of patients in our study (64.4%) received aminoglycosides 2-3 days/week. The incidence reported in this study is more similar to a study in MDR TB patients in Latvia which reported an incidence of 28% (52). The majority of patients received kanamycin, which is considered therapeutically interchangeable with amikacin which was the most common in this patient population, however no data on dosage or frequency

of delivery is given. None of the studies in the US nor the study in Latvia reported their definition of hearing loss or ototoxicity, so comparability between the incidence rates is weak.

Cumulative dosage is considered to be the most important risk factor for aminoglycoside induced-ototoxicity, however, only one identified study in Botswana reported a significant association between cumulative dosage and ototoxicity (23). The authors used classification and regression tree (CART) analyses, which classifies the data based on the association between potential predictors and the outcome. A binomial GINI coefficient is used to classify the data on significant predictors of ototoxicity. This methodology allows for analysis if there is high collinearity. This regression methodology produces a classification tree, but it does not produce odds ratios or other measures of association, so the results are not directly comparable to this study. A study in pulmonary non-tuberculosis mycobacterium (NTM) identified a significant negative association between total duration of treatment and ototoxicity (OR = 0.98, 95% CI: 0.8–1.13, p = 0.8)(31). The authors believed the association was negative as patients with early signs of hearing loss had early cessation of treatment. This reported association does not correspond with the findings of this study of an increased odds of ototoxicity with an increased duration of treatment. There was no indication that treatment in this study population was stopped early due to signs of hearing loss, which may explain the difference in the associations

A few other factors were identified as independently and significantly associated with ototoxicity risk in our cohort of hospitalized patients: gender, previous history of TB, and study site (duration model only). In both models, males had a 4-fold higher odds of ototoxicity compared to females (OR 4.4, 95% CI 1.2, 16.1; cumulative dose model and OR = 4.3, 95% CI 1.3, 14.2, p = 0.02; duration model). The mechanisms underlying an increased risk for males is unclear and the support in the literature is limited. A previous study in MDR TB patients in the UK also identified male gender as a risk factor for ototoxicity (p= 0.03) (24). Two other studies identifying risk factors for ototoxicity in MDR TB or NTB mycobacterium reported gender was not a significant risk factor (23,31). Previous history of TB also increased the odds of ototoxicity 2.7 times

compared to new cases of TB in the model with cumulative dose of aminoglycosides (95% CI 0.87, 8.48, p = 0.09). No previous studies of ototoxicity in TB reported an association with a history of TB. However, multiple studies in cystic fibrosis (CF) patients demonstrated an association between higher lifetime exposure to aminoglycosides and ototoxicity (28,29). Therefore, the association in this study may reflect past exposure to aminoglycosides, although history of aminoglycoside exposure was not statistically significant. It is unclear how extensive the treatment history collected was, so there may be misclassification of past aminoglycoside exposure.

In the model examining aminoglycosides categorized by total duration of exposure, the odds of ototoxicity was 6.23 times higher among patients at UTHSCT compared to patients at TCID/AGHH (95% CI 1.5,25.77, p = 0.01). The patients the UTHSCT had a significantly higher cumulative dosage and duration of treatment, which likely accounts for the increased risk among UTHSCT patients (χ^2 = 24.00, p= 0.0003, χ^2 = 22.00, p= 0.01). Also, the median cumulative dosage and total duration for TCID/AGHH patients were below the cutoffs for the dichotomous categorization of both exposures (39 g, IQR (14g, 67 g), 82.5 days, IQR (32.5 days,179 days)).

HIV status was expected to have a significant association with ototoxicity as it had been identified in the literature as a potential risk factor. However, the number of HIV patients in the study was relatively small due to the analytic sample containing only patients with therapeutic drug monitoring. It was unexpected that capreomycin was significantly associated with ototoxicity in the bivariate analysis, while amikacin was not significantly associated. Capreomycin is thought to be less ototoxic than amikacin or kanamycin. The association with amikacin and ototoxicity may not have been significant as the majority of patients received amikacin (87.7%, Table 3) and all patients, except for one, who received multiple aminoglycosides received amikacin. Therefore, the association may be confounded by the other aminoglycosides given to patients receiving amikacin.

STRENGTHS AND LIMITATIONS

The population for this study was restricted to patients hospitalized for TB with therapeutic drug monitoring and at least 2 audiograms. Therefore, it may not be generalizable beyond this population. The main limitation of this study is in the small or zero cells for multiple covariates of interest. This prevented the inclusion of potentially significant covariates in the multivariate model. It also inflated the confidence intervals for the bivariate and univariate analyses. The small cells also prevented stratification of multivariate model, which was appropriate based off the descriptive and bivariate analysis. The study was also limited because the audiograms were not taken systematically or at regular intervals. Ototoxicity may be being detected weeks to months following onset, leading to information bias in time-dependent variables. Creatinine rise was reported as significant in multiple studies in the literature, but could not be investigated in this study as data on it was missing for all patients from the UTHSCT study site.

Despite these limitations, this study contained a rich dataset with an in depth information on clinical and demographic characteristics for patients. The data were also collected in a longitudinal format with serial audiograms. Few studies examining ototoxicity in TB patients have examined the association with this level of detail. A strength of the study population is it is it may be representative of hospitalized TB cases in the United States, where monitoring of aminoglycoside treatment is most easily facilitated.

FUTURE DIRECTIONS AND IMPACT ON PUBLIC HEALTH

The results of this analysis and the literature review suggest that cumulative dosage of aminoglycosides is an important predictor of ototoxicity. Therefore, providers should consider carefully and routinely monitoring the level of total exposure to aminoglycosides among patients and perform regular hearing evaluations. However, further study of aminoglycoside-induced ototoxicity is necessary to understand the risk for patients receiving TB treatment before treatment guidelines can be changed. Additional studies are needed to replicate the results in

larger study populations and in different TB treatment settings. As the association between cumulative aminoglycoside dosage and ototoxicity appears to not be dose-dependent but based on a threshold, further study to determine a more appropriate or clinically relevant threshold may be warranted. The threshold in this study was arbitrarily chosen as the third quartile.

Increased monitoring of patients with a history of TB and/or male patients may also be warranted the results show they are at an increased risk. As the odds of ototoxicity are only statistically significant only above a threshold, reducing the length or total dosage of aminoglycoside treatment may lower the incidence of ototoxicity among TB patients. If the total dosage cannot be effectively reduced and maintaining treatment efficacy, it may be worthwhile to consider providing capreomycin instead of amikacin to TB patients in the US indicated for treatment regimens containing aminoglycosides, as it is known to be less ototoxic. Previous studies have advocated that it may be more ethically appropriate to remove aminoglycosides from TB treatment regimens all together, as ototoxicity is a severe and permanent adverse event and is still not well understood. Bedaquiline and Delamanid have been proposed as replacements for aminoglycosides in MDR TB regimens, but study of their efficacy in a regimen without aminoglycosides is still ongoing.

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TABLES

Table 2. Summary of Incidence of Ototoxicity in Tuberculosis and non-Tuberculosis *mycobacterium* Reported in Literature Based on Literature Search of Aminoglycoside Induced Ototoxicity Using Pubmed, March 2018

First Author	Study Year	Country	Study Size	Overall n (%)	Amikacin n (%)	Kanamycin n (%)	Capreomycin n (%)	Streptomycin n (%)
Baghaei (47)	2006-2009	Iran	80		14 (10%)			
Modongo (23)	2011-2012	Botswana	28		11 (39%)			
Bloss (53)	2000-2004	Latvia	1027	195 (19%)				
Dheda (12)		South Africa	199	10 (6%)				
Furin (54)	1996-1999	Peru	60	4 (6.7%)				
Geerling (55)	1985-1998	Netherlands	44	0-6* (0-14%)				
Isaskidis[+] (10)	2007-2011	India	58				5 (9%)	
Jacob (41)	2002-2007	Belgium	23		11 (50%)			
Joseph (9)		India	38		1 (2.6%)			
Keshavjee (56)	2000-2004	Russia	636	75 (13%)				
Kim (57)	1996-2005	South Korea	211	8 (3.8%)				
Leimane (52)	2000	Latvia	204	58 (28%)				
Malla (11)	2005-2006	Nepal	175	12 (9.6%)				
Masjedi (58)	2002-2006	Iran	43		20 (46%)			
Nathanson (59)	1998-2002	Multi-Country	818	98 (12%)				
Tupasi (60)	1999-2002	Philippines	117	22 (19%)		26	1	5
Uffredi (61)	1998-1999	France	45	2 (4.4%)				
Van Deun (40)	1997-2007	Bangladesh	427			19 (4.4%)		
Yew (62)	1990-1997	Hong Kong	63	9 (14%)				
Yang (42)	1992-2004	South Korea	256	110 (41.8%)				
Arnold (24)	2008-2015	United Kingdom	93	55 (59%)	28 (52.8%)		2 (5.4%)	
Burgos (45)	1982-2000	United States	48			2 (7.6%)		1 (3.6%)
Chan (44)	1984-1998	United States	205		8 (11%)	9 (8.6%)	4 (2.8%)	
Tahaoglu (63)	1992-1999	Turkey	158		40 (33%)	2 (13%)	3 (20%)	2 (25%)
Telzak (46)	1994	United States	26	1 (5.8%)	0	1 (50%)	0	
Goble (43)	1973-1983	United States	171		1 (16.7%)	10 (14%)	4 (3.7%)	0
Duggal (25)	2000-2006	India	64	18.75%	7 (20.6%)	4 (15.4%)	1 (25%)	
Vasconcelos (64)	2008	Brazil	97	54 (55.7%)				

First Author	Study Year	Country	Study Size	Overall Ototoxicity	Amikacin n (%)	Kanamycin n (%)	Capreomycin n (%)	Streptomycin n (%)
Harris (65)		South Africa	153	87 (58%)				
Mondongo	2006-2012	Botswana	437		270 (62%)			
Pediatric TB Studies								
Drobac (66)	2009-2003	Peru	38	2 (7%)				
Ghafari (27)	2010	South Africa	29	12 (48%)				
Non–tuberculosis *Mycobacterial* disease								
Ellender (31)	2002-2012	Australia	45		8 (18%)			
Namkoong (32)	2004-2013	Japan	13	0 (0%)				
Klis (33)	2006-2009	Ghana	127					Adults: 13 (31%) Children: 23 (27%)

[+]Among HIV + patients

*Unable to calculate from results

Table 3. Sociodemographic and Clinical Characteristics of Patients of 81 Patients with Therapeutic Drug Monitoring for Tuberculosis and at least 2 Audiograms During Admission, 1985-2015. Values are n (%) unless otherwise specified.					
	Overall (N = 81)	UTHSCT (n =33)	Other Sites (TCID & AGHH) (n =48)	Chi Squared Value	p-value
Characteristics	n (%)	n (%)	n (%)		
Age, years (Mean, SD)	42.93 (17.0)	44.18 (14.2)	42.06 (18.8)	0.30 ±	0.59
Age category					
18-24	9 (11.1)	2 (6.1)	7 (14.6)	0.41+	0.41
25-34	22 (27.2)	7 (21.2)	15 (31.3)		
35-44	18 (22.2)	10 (30.3)	8 (16.7)		
45-54	11 (13.6)	5 (15.2)	6 (12.5)		
55-64	12 (14.8)	6 (18.2)	6 (12.5)		
≥ 65	9 (11.1)	3 (9.1)	6 (12.5)		
Sex					
Female	22 (27.2)	8 (24.2)	14 (29.2)	0.24	0.62
Male	59 (72.8)	25 (75.8)	34 (70.8)		
Race					
White	18 (22.5)	10 (31.3)	8 (16.7)	0.002	0.29
Black	13 (16.3)	6 (18.8)	7 (14.6)		
Hispanic	36 (45.0)	13 (40.6)	23 (47.9)		
Other	13 (16.23)	3 (9.4)	10 (20.8)		
Place of Birth					
US	29 (37.2)	16 (51.6)	13 (27.7)	4.59	0.03*
Non-US	49 (62.8)	15 (48.4)	34 (72.3)		
Weight, lbs (Mean, SD)	131.54 (26.2)	124.19 (27.4)	136.44 (24.4)	4.38±	0.04*
Previous TB					
No	39 (48.2)	22 (66.7)	17 (35.4)	7.65	0.01*
Yes[a]	42 (51.9)	11 (33.3)	31 (64.6)		
Previous treatment with Aminoglycosides, any indication					
No	53 (75.7)	19 (73.1)	34 (77.3)	0.16	0.69
Yes	17 (24.3)	7 (26.9)	10 (22.7)		

Characteristics	Overall (N = 81)	UTHSCT (n =33)	Other Sites (TCID & AGHH) (n =48)	Chi Squared Value	p-value
	n (%)	n (%)	n (%)		
HIV Status					
HIV-	71 (87.7)	29 (87.9)	42 (87.5)	0.08[+]	0.57
HIV+	7 (8.6)	2 (6.1)	5 (10.4)		
Unknown	3 (3.7)	2 (6.1)	1 (2.1)		
Diabetes					
No	61 (77.2)	25 (80.7)	36 (75.0)	0.34	0.56
Yes	18 (22.8)	6 (19.4)	12 (25.0)		
Smoking Status					
Never	37 (46.2)	12 (37.5)	25 (52.1)	1.98	0.37
Current	26 (32.5)	13 (40.6)	13 (27.1)		
Former	17 (21.3)	7 (21.9)	10 (20.8)		
Alcohol Use					
None	48 (60.8)	25 (78.1)	23 (48.9)	6.80	0.01*
Yes [b]	31 (39.2)	7 (21.9)	24 (51.1)		
IV Drug Use					
No	71 (93.4)	28 (90.3)	43 (95.6)	0.24[+]	0.39
Yes[b]	5 (6.6)	3 (9.7)	2 (4.4)		
Current TB Episode: Type					
Pulmonary	72 (91.1)	29 (87.9)	43 (93.5)	0.21[+]	0.44
Extra-Pulmonary	7 (8.9)	4 (12.1)	3 (6.5)		
Current TB Episode: Drug Resistance					
Drug-Susceptible TB	19 (23.5)	8 (24.2)	11 (22.9)	0.02	0.89
MDR/RR TB	62 (76.5)	25 (75.8)	37 (77.1)		
Current TB Episode: TB Treatment with Aminoglycosides[c]					
None	10 (12.4)	1 (3.1)	9 (18.8)	0.03[+]	0.04*
Any	71 (87.7)	32 (97.0)	39 (81.3)		

Characteristics	Overall (N = 81)	UTHSCT (n =33)	Other Sites (TCID & AGHH) (n =48)	Chi Squared Value	p-value
	n (%)	n (%)	n (%)		
Amikacin					
No	27 (33.3)	13 (39.4)	14 (29.2)	0.92	0.34
Yes	54 (66.7)	20 (60.6)	34 (70.8)		
Kanamycin					
No	78 (96.3)	31 (93.9)	47 (97.9)	0.30[+]	0.56
Yes	3 (3.7)	2 (6.1)	1 (2.1)		
Capreomycin					
No	52 (64.2)	10 (30.3)	42 (87.5)	27.83	<.0001*
Yes	29 (35.8)	23 (69.7)	6 (12.5)		
Streptomycin					
No	64 (79.0)	21 (63.6)	43 (89.6)	7.94	0.005*
Yes	17 (21.0)	12 (36.4)	5 (10.4)		
Current TB Episode: Number of total aminoglycosides used					
0	10 (12.4)	1 (3.0)	9 (18.8)	<0.001[+]	<0.001*
1	44 (54.3)	12 (36.4)	32 (66.7)		
2	22 (27.2)	15 (45.5)	7 (14.6)		
3	5 (6.2)	5 (15.2)	0 (0)		
Number of changes in Aminoglycoside, median (IQR)	0 (0-1)	1 (0-3)	0 (0-0)	21.28[T]	0.0001*
Number of changes in Aminoglycoside[d]					
0	56 (69.1)	16 (48.5)	40 (83.3)	<.0001[+]	0.01*
1	6 (7.4)	4 (12.1)	2 (4.2)		
2	7 (8.6)	4 (12.1)	3 (6.3)		
3	6 (7.4)	5 (15.2)	1 (2.1)		
≥4	6 (7.4)	4 (12.1)	2 (4.2)		

Characteristics	Overall (N = 81)	UTHSCT (n =33)	Other Sites (TCID & AGHH) (n =48)	Chi Squared Value	p-value
	n (%)	n (%)	n (%)		
Total Duration Aminoglycosides, days (median, IQR)	105 (47-435)	429 (70-734)	82.5 (32.5-179)	22.00ᵀ	0.01*
Current Aminoglycoside Delivery Route[e]					
Intramuscular	151 (43.1)	71(38.2)	80 (48.8)	4.00	0.05*
Intravenous	199 (56.9)	115 (61.8)	84 (51.2)		
Current TB Episode: Aminoglycoside Dosage, mg (median, IQR)[e]	600 (500-750)	550 (425-750)	700 (500-765)	97.38ᵀ	0.0003*
Current TB Episode: Current Aminoglycoside Dosage (mg)[e]					
<400	27 (7.7)	27 (14.4)	0 (0)	27.96	<.0001*
400 - 599	134 (38.2)	72 (38.5)	62 (37.8)		
600 - 799	122 (34.8)	59 (31.6)	63 (38.4)		
>= 800	68 (19.4)	29 (15.5)	39 (23.8)		
Current TB Episode: Cumulative Aminoglycoside Dosage (mg) (median, IQR)	48000 (21000-167000)	147500 (39000-254875)	38875 (14025-67000)	24.00ᵀ	0.0003*
Current TB Episode: Cumulative Aminoglycoside Dosage (mg)					
0	10 (12.4)	1 (3.03)	9 (18.8)	13.59	0.004*
< 32000	17 (21.0)	6 (18.2)	11 (22.9)		
32000-18375	37 (45.7)	13 (39.4)	24 (50)		
> 181375	17 (21.0)	13 (39.4)	4 (8.3)		

Characteristics	Overall (N = 81)	UTHSCT (n =33)	Other Sites (TCID & AGHH) (n =48)	Chi Squared Value	p-value
	n (%)	n (%)	n (%)		
Current Aminoglycoside Frequency[e]					
5-7 times/week (daily)	87 (35.2)	11 (9.7)	76 (56.7)	<0.001[+]	<0.001*
2-3 times/week	159 (64.4)	102 (90.3)	57 (42.5)		
1 time/week	1 (0.4)	0 (0)	1 (0.8)		
Current TB Episode: Treatment with First Line Drugs					
No	13 (16.1)	4 (12.1)	9 (18.8)	0.64	0.42
Yes	68 (84.0)	29 (87.9)	39 (81.3)		
Current TB Episode: Other Second Line Drugs[f]					
None	13 (16.0)	5 (15.2)	8 (16.7)	0.002[+]	0.19
Fluoroquinolones	27 (33.3)	10 (30.3)	17 (35.4)		
Oral Bacteriostatic Agents	36 (44.4)	18 (54.6)	18 (37.5)		
Agents with Unclear Role	5 (6.2)	0 (0)	5 (10.4)		
Ototoxicity[g]					
None	54 (66.7)	14 (42.4)	40 (83.3)	14.73	0.0001*
Any	27 (33.3)	19 (57.6)	8 (16.7)		
Ototoxicity, Location[g]					
None	54 (66.7)	14 (42.4)	40 (83.3)	<0.0001[+]	0.0003*
Unilateral only	5 (6.2)	3 (9.1)	2 (4.2)		
Bilateral	22 (27.2)	16 (48.5)	6 (12.5)		
Other Adverse Events					
None	72 (88.9)	26 (78.8)	46 (95.8)	0.02[+]	0.02*
Any	9 (11.1)	7 (21.2)	2 (4.2)		

Characteristics	Overall (N = 81)	UTHSCT (n =33)	Other Sites (TCID & AGHH) (n =48)	Chi Squared Value	p-value
	n (%)	n (%)	n (%)		
Adverse Event: Night Sweats					
No	78 (96.3)	30 (90.9)	48 (100)	0.06[+]	0.06*
Yes	3 (3.7)	3 (9.1)	0 (0)		
Gastrointestinal					
No	77 (95.1)	29 (87.9)	48 (100)	0.02[+]	0.02*
Yes	4 (4.9)	4 (12.1)	0 (0)		
Thrombocytopenia					
No	80 (98.8)	33 (100)	47 (97.9)	0.59[+]	1
Yes	1 (1.2)	0 (0)	1 (2.1)		
Vision Loss					
No	79 (97.5)	31 (93.9)	48 (100)	0.16[+]	0.16
Yes	2 (2.5)	2 (6.1)	0 (0)		
Hypothyroidism					
No	80 (98.77)	33 (100)	47 (97.92)	0.59[+]	1
Yes	1 (1.23)	0 (0)	1 (2.08)		
Loss of Taste					
No	80 (98.8)	32 (97.0)	48 (100)	0.41[+]	0.41
Yes	1 (1.2)	1 (3.0)	0 (0)		
Current TB Episode: Treatment Outcome[h]					
Cured	26 (32.1)	10 (30.3)	16 (33.3)	<0.001[+]	<0.001*
Completed treatment	6 (7.4)	6 (18.2)	0 (0)		
Failed treatment	12 (14.8)	11 (33.3)	1 (2.1)		
Died	3 (3.7)	3 (9.1)	0 (0)		
Drop Out	3 (3.7)	1 (3.0)	2 (4.2)		
Indeterminate	31 (38.3)	2 (6.1)	29 (60.4)		

Current TB Episode: Reason for Indeterminate Outcome					
Missing	1 (3.2)	1 (50.0)	0 (0)		
Treatment Continued	30 (96.8)	1 (50.0)	29 (100.0)		

Abbreviations: UTHSCT = University of Texas Health Science Center , TCID = Texas Center for Infectious Diseases, AGHH = A.G. Holley Hospital University of Texas Health Science Center , SD = standard deviation, IQR = interquartile range, TB = Tuberculosis, HIV = Human Immunodeficiency Virus, IV = intravenous, MDR =multidrug resistant , RR = rifampin resistant

+ Fisher's Exact Test, ± ANOVA F-Test, ⊤ Median Test

* Significant test of independence ($\alpha = 0.05$)

[a] Includes relapsed, recurrent and history of occult TB

[b] Includes current and former

[c] Any aminoglycoside given during the current admission before the last audiogram was measured

[d] A change was defined as a different aminoglycoside started on a date following the previous instance of aminoglycoside treatment

[e] Calculated for all aminoglycosides given during the current admission

[f] Defined based off of grouping in Table 1.

[g] Defined as at least a 20 dB increase at any one frequency, 10 dB at two adjacent frequencies or an audiogram at 4 months after start of aminoglycoside treatment or later and at least one frequency greater than 40 dB

[h] Based off of World Health Organization treatment outcome definitions

Table 4. Bivariate Associations Between Sociodemographic and Clinical Characteristics and Ototoxicity Among 81 Patients with Therapeutic Drug Monitoring for Tuberculosis and at least 2 Audiograms During Admission, 1985-2015. [a] **Ototoxicity was defined as at least a 20 dB increase at any one frequency, 10 dB at two adjacent frequencies or an audiogram at 4 months after start of aminoglycoside treatment or later and at least one frequency greater than 40 dB**

	No Ototoxicity (n =54)	Ototoxicity (n=27)	Overall (N = 81			UTHSCT (n = 33			TCID/AGHH (n = 45)		
Characteristic	n (%)	n (%)	Odds Ratio	95% Confidence Interval (CI)	p-value	Odds Ratio	95% Confidence Interval (CI)	p-value	Odds Ratio	95% Confidence Interval (CI)	p-value
Age, years (mean, SD)	41.94 (17.59)	44.85 (16.01)	1.01	(0.98, 1.04)	0.47	1.01	(0.96, 1.06)	0.67	1.01	(0.97, 1.05)	0.70
Age category											
18-24	6 (11.11)	3 (11.11)	Ref			Ref			Ref		
25-34	16 (29.63)	6 (22.22)	0.75	(0.14, 4.00)	0.60	2.50	(0.1, 62.6)	0.39	0.18	(0.01, 2.43)	0.27
35-44	13 (24.07)	5 (18.52)	0.77	(0.14, 4.33)	0.66	0.67	(0.03, 14.03)	0.30	0.36	(0.03, 5.11)	0.77
≥ 45	19 (35.19)	13 (48.15)	1.37	(0.29, 6.48)	0.31	1.80	(0.09, 35.42)	0.61	0.71	(0.10, 5.18)	0.47
Sex											
Female	18 (33.33)	4 (14.81)	Ref			Ref			Ref		
Male	36 (66.67)	23 (85.19)	2.87	(0.86, 9.58)	0.04*	1.48[+]	(0.22, 10.06)	0.92	5.56[±]	(1.02, Inf)	0.05*
Race											
White	10 (18.52)	8 (30.77)	Ref			Ref			Ref		
Black	9 (16.67)	4 (15.38)	0.56	(0.12, 2.49)	0.93	0.24[+]	(0.01, 2.76)	0.36	2.61[+]	(0.11, 188.36)	0.89
Hispanic	24 (44.44)	12 (46.15)	0.62	(0.2, 1.99)	0.66	0.52[+]	(0.06, 3.73)	0.73	1.91[+]	(0.16, 104.92)	1.00
Other	11 (20.37)	2 (7.69)	0.23	(0.04, 1.33)	0.17	0.87[+]	(0.03, 67.23)	1	0.8[±]	(0, 15.2)	0.44
Place of Birth											
US	16 (30.19)	13 (52)	0.40	(0.15, 1.06)	0.07	1.17	(0.28, 4.87)	0.83	0.22	(0.04, 1.16)	0.07
Non-US	37 (69.81)	12 (48)	Ref			Ref			Ref		
Weight, lbs	132.82 (25.96)	128.50 (26.83)	0.99	(0.98, 1.01)	0.49	1.01	(0.98, 1.04)	0.92	1.01	(0.98, 1.04)	0.66
Previous TB											
No	20 (37.04)	19 (70.37)	Ref			Ref			Ref		
Yes[b]	34 (62.96)	8 (29.63)	0.25	(0.09, 0.67)	0.01*	0.27	(0.06, 1.22)	0.09	0.48	(0.1, 2.24)	0.35

Characteristic	No Ototoxicity (n =54)	Ototoxicity (n=27)	Overall (N = 81)			UTHSCT (n = 33)			TCID/AGHH (n = 45)		
	n (%)	n (%)	Odds Ratio	95% Confidence Interval (CI)	p-value	Odds Ratio	95% Confidence Interval (CI)	p-value	Odds Ratio	95% Confidence Interval (CI)	p-value
Previous AG treatment											
No	40 (78.43)	13 (68.42)	Ref			Ref			Ref		
Yes	11 (21.57)	6 (31.58)	1.68	(0.52, 5.44)	0.39	3.44	(0.53, 22.43)	0.20	0.64	(0.07, 6.26)	0.70
HIV Status											
HIV-	47 (87.04)	23 (85.19)	0.34	(0.04, 3)	0.11	0.34±	(0, 2.98)	0.21	1.24+	(0.02, 15.45)	1
HIV+	6 (11.11)	1 (3.7)	Ref			Ref			Ref		
Unknown	1 (1.85)	3 (11.11)	6.13	(0.6, 62.22)	0.07	2.64±	(0.38, inf)	0.22	5.14±	(0,97.71)	0.84
Diabetes											
No	40 (74.07)	21 (84)	Ref			Ref			Ref		
Yes	14 (25.93)	4 (16)	0.54	(0.16, 1.86)	0.33	0.79	(0.13, 4.68)	0.79	0.38	(0.04, 3.42)	0.39
Smoking Status											
Never	28 (51.85)	8 (32)	Ref			Ref			Ref		
Current	15 (27.78)	11 (44)	2.57	(0.85, 7.76)	0.23	0.97	(0.19, 4.87)	0.91	5.11	(0.79, 32.96)	0.17
Former	11 (20.37)	6 (24)	1.91	(0.54, 6.78)	0.76	1.11	(0.16, 7.51)	0.89	2.87	(0.35, 23.92)	0.79
Alcohol Use											
Never	32 (59.26)	15 (62.5)	Ref			Ref			Ref		
Yes[c]	22 (40.74)	9 (37.5)	0.87	(0.32, 2.35)	0.79	1.13	(0.21, 6.17)	0.89	2.76	(0.48, 15.95)	0.26
IV Drug Use											
No	48 (90.57)	22 (100)	Ref			Ref			Ref		
Yes[c]	5 (9.43)	0 (0)	0.34±	(0,1.94)	0.17	0.20±	(0, 1.41)	0.09	2.70±	(0, 23.81)	0.75
Current TB Episode: Type											
Pulmonary	47 (90.38)	25 (92.59)	Ref			Ref			Ref		
Extra-Pulmonary	5 (9.62)	2 (7.41)	0.75	(0.14, 4.16)	0.74	0.71+	(0.05, 11.13)	1	1.21±	(0, 8.53)	0.56

Characteristic	No Ototoxicity (n =54)	Ototoxicity (n=27)	Overall (N = 81)			UTHSCT (n = 33)			TCID/AGHH (n = 45)		
	n (%)	n (%)	Odds Ratio	95% Confidence Interval (CI)	p-value	Odds Ratio	95% Confidence Interval (CI)	p-value	Odds Ratio	95% Confidence Interval (CI)	p-value
Current TB Episode: Drug Resistance											
DS TB	16 (29.63)	3 (11.11)	Ref			Ref			Ref		
MDR/RR TB	38 (70.37)	24 (88.89)	3.37	(0.89, 12.8)	0.07	18.00	(1.86, 174.21)	0.01*	0.87	(0.15, 5.08)	0.88
Current TB Treatment with IAs[d]											
None	8 (14.81)	2 (7.41)	Ref			Ref			Ref		
Any	46 (85.19)	25 (92.59)	2.17	(0.43,11.31)	0.35	1.36±	(0,25.79)	0.58	1.73+	(0.18,88.59)	1
Amikacin											
No	20 (37.04)	7 (25.93)	Ref			Ref			Ref		
Yes	34 (62.96)	20 (74.07)	1.68	(0.6, 4.67)	0.32	3.73	(0.86, 16.25)	0.08	1.29	(0.23, 7.31)	0.78
Kanamycin											
No	54 (100)	24 (88.89)	Ref			Ref			Ref		
Yes	0 (0)	3 (11.11)	8.21±	(1.22, Inf)	0.03*	1.84±	(0.21, Inf)	032	5.00±	(0.26, Inf)	0.17
Capreomycin											
No	41 (75.93)	11 (40.74)	Ref			Ref			Ref		
Yes	13 (24.07)	16 (59.26)	4.59	(1.71, 12.34)	0.003 *	5.03+	(0.84, 39.55)	0.08	0.56±	(0, 3.31)	0.31
Streptomycin											
No	43 (79.63)	21 (77.78)	Ref			Ref			Ref		
Yes	11 (20.37)	6 (22.22)	1.12	(0.36, 3.43)	0.85	0.20	(0.04, 0.92)	0.04*	4.11	(0.56, 29.96)	0.16

Characteristic	No Ototoxicity (n =54)	Ototoxicity (n=27)	Overall (N = 81)			UTHSCT (n = 33)			TCID/AGHH (n = 45)		
	n (%)	n (%)	Odds Ratio	95% Confidence Interval (CI)	p-value	Odds Ratio	95% Confidence Interval (CI)	p-value	Odds Ratio	95% Confidence Interval (CI)	p-value
Amikacin or Kanamycin											
No	20 (37.04)	6 (22.22)	Ref			Ref			Ref		
Yes	34 (62.96)	21 (77.78)	2.06	(0.71,5.96)	0.18	3.73	(0.86,16.25)	0.08	3.00	(0.33,27.11)	0.33
Number of total AGs used											
0	8 (14.81)	2 (7.41)	Ref			Ref			Ref		
1	35 (64.81)	9 (33.33)	1.03	(0.19, 5.71)	0.14	0.62±	(0, 11.88)	0.38	1.47+	(0.13, 78.71)	1.00
2-3	11 (20.37)	16 (59.26)	5.82	(1.03,32.79)	0.002 *	2.50±	(0,47.50)	0.71	2.97+	(0.12,211.93)	0.8
Changes in AG (median, IQR)	0 (0)	1 (3)	1.26	(0.99,1.62)	0.07	1.36	(0.88,2.09)	0.16	0.97	(0.60,1.57)	0.91
Changes in AG[e]											
0	44 (81.48)	12 (44.44)	Ref			Ref			Ref		
1	3 (5.56)	3 (11.11)	3.67	(0.65, 20.54)	0.93	0.45+	(0.01,7.07)	0.93	13.73 ±	(1.57,Inf)	0.02*
2	2 (3.7)	5 (18.52)	9.17	(1.58, 53.26)	0.24	5.65±	(0.85,Inf)	0.07	3.36+	(0.05,76.5)	0.74
3	2 (3.7)	4 (14.81)	7.33	(1.2, 44.96)	0.40	4.77+	(0.36,280.81)	0.37	7.20±	(0,136.70)	0.88
≥4	3 (5.56)	3 (11.11)	3.67	(0.65, 20.54)	0.93	3.61+	(0.23,224.54)	0.58	3.09±	(0,27.51)	0.77
Total Duration AGs, days (mean, SD)[f]	140.4 (204.96)	569.33 (605.39)	1.00	(1.00, 1.01)	0.0001 *	1.00	(1.00, 1.01)	0.01*	1.00	(1.00, 1.01)	0.20

Characteristic	No Ototoxicity (n =54)	Ototoxicity (n=27)	Overall (N = 81)			UTHSCT (n = 33)			TCID/AGHH (n = 45)		
	n (%)	n (%)	Odds Ratio	95% Confidence Interval (CI)	p-value	Odds Ratio	95% Confidence Interval (CI)	p-value	Odds Ratio	95% Confidence Interval (CI)	p-value
Total Duration AGs, days[f]											
< 47	16 (19.8)	4 (4.9)	Ref			Ref			Ref		
47-435	33 (40.7)	8 (9.9)	0.97	(0.25,3.71)	0.02*	0.67	(0.08,5.68)	0.07	1.08	(0.17,6.73)	0.43
>435	5 (6.2)	15 (18.5)	12.00	(2.7,53.33)	<0.001*	9.75	(0.95,99.96)	0.01*	4.33	(0.42,44.43)	0.16
Median AG Dosage (mg) (median, IQR)[f]	675 (250)	750 (200)	1.00	(1, 1)	0.78	1.00	(0.99, 1)	0.05*	1.01	(1, 1.01)	0.03*
Max AG Dosage (mg) (median, IQR)[f]	750 (400)	750 (250)	1.00	(1, 1)	0.13	1.00	(1, 1)	0.76	1.01	(1, 1.01)	0.03*
Cumulative AG Dosage (mg) (median, IQR)	39750 (53375)	181375 (183150)	1.00	(1.00,1.00)	0.0001*	1.00	(1.00,1.00)	0.01*	1.00	(1.00,1.00)	0.09
Cumulative AG Dosage (mg)											
0	8 (14.81)	2 (7.41)	Ref			Ref			Ref		
< 32000	16 (29.63)	1 (3.70)	0.25	(0.02,3.19)	0.29	0.04[±]	(0, 7.60)	0.29	0.82[±]	(0,15.55)	0.45
32000-181375	26 (48.15)	11 (40.74)	1.69	(0.31,9.29)	0.54	1.00[±]	(0,19.00)	0.50	2.06[+]	(0.18,111.84)	0.93
>181375	4 (7.41)	13 (48.15)	13.00	(1.92,87.99)	0.01*	6.00[±]	(0,114.00)	0.86	6.52[+]	(0.23,529.16)	0.41

Characteristic	No Ototoxicity (n =54)	Ototoxicity (n=27)	Overall (N = 81)			UTHSCT (n = 33)			TCID/AGHH (n = 45)		
	n (%)	n (%)	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Current AG Delivery Route[f]											
None	8 (14.81)	2 (7.41)	Ref			Ref			Ref		
IM Only	21 (38.89)	10 (37.04)	2.46	(0.41,14.63)	0.47	0.33±	(-inf,1.07)	0.79	0.35±	(-inf, 1.09)	0.80
IV Only	13 (24.07)	8 (29.63)	1.91	(0.34,10.67)	0.90	0.61±	(-inf,1.34)	0.92	0.38+	(-1.26,2.01)	1.00
Both	12 (22.22)	7 (25.93)	2.33	(0.38,14.23)	0.57	1.01±	(-inf,1.74)	0.98	0.82+	(-inf,1.56)	0.96
Current AG Frequency[f]											
None	8 (14.81)	2 (7.41)	Ref			Ref			Ref		
5-7 times/week Only	15 (27.78)	5 (18.52)	1.33	(0.21,8.49)	0.64	1.00±	(0,19.00)	0.50	1.43+	(0.06,96.39)	1.00
2-3 times/week Only	10 (18.52)	5 (18.52)	2.00	(0.30,13.17)	0.70	1.00±	(0,19.00)	0.50	2.52+	(0.11,176.4)	0.91
Multiple Frequencies	21 (38.89)	15 (55.56)	2.86	(0.5,15.41)	0.15	2.17±	(0,41.17)	0.68	1.57+	(0.11,94.35)	1.00
Treatment with First Line Drugs											
No	9 (16.67)	4 (14.81)	Ref			Ref			Ref		
Yes	45 (83.33)	23 (85.19)	1.15	(0.32,4.14)	0.83	0.41	(0.04,4.43)	0.46	1.75	(0.19,16.34)	0.62

Characteristic	No Ototoxicity (n =54)	Ototoxicity (n=27)	Overall (N = 81)			UTHSCT (n = 33)			TCID/AGHH (n = 45)		
	n (%)	n (%)	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Treatment Other Second Line Drugs											
None	11 (20.37)	2 (7.41)	Ref			Ref			Ref		
Fluoro-quinolones	19 (35.19)	8 (29.63)	2.27[+]	(0.36,25.73)	0.57	3.66[+]	(0.24.235.67)	0.59	1.48[+]	(0.10,89.84)	1.00
Oral Bacteriostatic Agents	19 (35.19)	17 (62.96)	4.78[+]	(0.86,50.45)	0.08	9.26[+]	(0.70,550.31)	0.11	1.95[+]	(0.15,112.36)	1.00
Agents with Unclear Role	5 (9.26)	0 (0)	1.04[±]	(0,9.35)	0.51				1.60[±]	(0,30.40)	0.62
Other Adverse Events											
None	52 (96.3)	20 (74.07)	Ref			Ref			Ref		
Any	2 (3.7)	7 (25.93)	9.10	(1.74, 47.57)	0.01*	6.00	(0.63, 57.02)	0.12	5.57	(0.31, 99.88)	0.24
Adverse Event: Night Sweats											
No	54 (100)	24 (88.89)	Ref			Ref					
Yes	0 (0)	3 (11.11)	8.21[±]	(1.22,Inf)	0.03*	3.09[±]	(0.44,Inf)	0.18			
Gastro - intestinal											
No	53 (98.15)	24 (88.89)	Ref			Ref					
Yes	1 (1.85)	3 (11.11)	6.62	(0.65, 67.01)	0.11	2.44	(0.23, 26.3)	0.46			

Characteristic	No Ototoxicity (n =54)	Ototoxicity (n=27)	Overall (N = 81)			UTHSCT (n = 33)			TCID/AGHH (n = 45)		
	n (%)	n (%)	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Thrombo-cytopenia											
No	54 (100)	26 (96.3)	Ref						Ref		
Yes	0 (0)	1 (3.7)	2.00±	(0.11,Inf)	0.33				5.00±	(0.26,Inf)	0.17
Vision Loss											
No	54 (100)	25 (92.59)	Ref			Ref					
Yes	0 (0)	2 (7.41)	4.97	(0.59,0)	0.11	1.84±	(0.21,inf)	0.32			
Hypo-thyroidism											
No	53 (98.15)	27 (100)	Ref						Ref		
Yes	1 (1.85)	0 (0)	2.00±	(0, 38)	0.68				5.00±	(0, 95.00)	0.83
Loss of Taste											
No	54 (100)	26 (96.3)	Ref								
Yes	0 (0)	1 (3.7)	2.00±	(0.11,Inf)	0.33	0.74±	(0.04,inf)	0.58			
Treatment Outcome[g]											
Cured	2 (3.7)	4 (14.81)	Ref			Ref			Ref		
Completed treatment	16 (29.63)	10 (37.04)	3.20	(0.49, 20.81)	0.13	1.31+	(0.11, 21.28)	1.00			
Failed treatment	7 (12.96)	8 (29.63)	1.83	(0.51, 6.61)	0.30	0.89+	(0.12, 6.07)	1.00	3.25±	(0, 61.75)	0.76
Indeterminate	29 (53.7)	5 (18.52)	0.28	(0.08, 0.95)	0.002 *	0.36+	(0, 9.27)	0.87	0.45+	(0.07, 2.87)	0.52

Reason for Indeterminate Outcome											
Missing						0.68±	(0.04, Inf)	0.59			
Treatment Continued			0.20	(0.06,065)	0.96	0.78±	(0, 14.78)	0.44	0.60	(0.13,2.76)	0.51

Abbreviations: UTHSCT = University of Texas Health Science Center , TCID = Texas Center for Infectious Diseases, AGHH = A.G. Holley Hospital University of Texas Health Science Center , SD = standard deviation, IQR = interquartile range, TB = Tuberculosis, HIV = Human Immunodeficiency Virus, IV = intravenous, DS = drug susceptible, MDR =multidrug resistant , RR = rifampin resistant, AG = aminoglycoside, Inf = Infinite

+ Exact Estimate, ±Median Unbiased Estimate from Exact Conditional Distribution

*Significant Wald Test ($\alpha = 0.05$)

[a] Sample consists of first observation of ototoxicity or last observation of subjects that did not experience ototoxicity

[b] Includes relapsed, recurrent and history of occult TB

[c] Includes current and former

[d] Any aminoglycoside given during the current admission before the last audiogram was measured

[e] A change was defined as a different aminoglycoside started on a date following the previous instance of aminoglycoside treatment

[f] Calculated for all aminoglycosides given during the current admission

[g] Based off of World Health Organization treatment outcome definitions with Failed and Dead combined into one category

Table 5. Multivariate Association of Ototoxicity and Cumulative Dosage of Any Aminoglycoside Treatment Among Patients with Therapeutic Drug Monitoring for TB, 1985-2015 (n=81)[a]

	Odds Ratio	95% CI	Regression Coefficient (SE)	p-value
Intercept			-6.17 (1.30)	<0.0001*
Cumulative Aminoglycoside Dosage	3.75	(1.42,9.96)	1.32 (0.50)	0.02*
Time[b]	1.31	(1.20, 1.43)	0.27 (0.04)	<.0001*
Age, years[c]	1.04	(1.00, 1.08)	0.04 (0.02)	0.05
Gender	4.40	(1.20, 16.11)	1.48 (0.66)	0.03*
Previous TB[d]	2.71	(0.87,8.48)	1.00 (0.58)	0.09

Abbreviations: CI = confidence interval, SE= standard error TB = Tuberculosis, HIV = Human Immunodeficiency Virus, AG = aminoglycoside, *Significant Estimate

[a] Sample consists of the first observation for each two period for each subject

[b] Defined as time from admission in two week periods

[c] Age at admission

[d] Includes relapsed, recurrent and former occult

Table 6a. Multivariate Association of Continuous Total Duration of Aminoglycoside Treatment and Ototoxicity Among Patients with Therapeutic Drug Monitoring for TB, 1985-2015 (n=81)[a]

	Odds Ratio	95% CI	Regression Coefficient (SE)	p-value
Intercept			-5.83 (2.57)	0.02*
Total Duration	1.00	(1, 1)	0.002 (0.001)	0.01*
Time[b]	1.32	(0.91, 1.92)	0.28 (0.19)	<.0001*
Age, years[c]	1.03	(0.99, 1.07)	0.03 (0.02)	0.23
Gender	7.10	(1.77, 28.55)	1.96 (0.71)	0.01*
Study Site[d]	3.03	(0.65, 14.16)	1.11 (0.79)	0.16
Median Dosage	1.00	(0.23, 4.44)	0.001 (0.002)	0.76

Abbreviations: CI = confidence interval, SE= standard error TB = Tuberculosis, HIV = Human Immunodeficiency Virus, AG = aminoglycoside, *Significant Estimate

[a] Sample consists of the first observation for each two week interval for each subject

[b] Defined as time from admission in two week periods

[c] Age at admission

[d] Study Site 1 is the UTHSCT, study site 2 is TCID/AGHH combined; Site 2 is the reference value

Table 6b. Multivariate Association of Dichotomous Total Duration of Aminoglycoside Treatment and Ototoxicity Among Patients with Therapeutic Drug Monitoring for TB, 1985-2015 (n=81)[a]

	Odds Ratio	95% CI	Regression Coefficient (SE)	p-value
Intercept			-3.47 (2.09)	0.1
Total Duration	2.74	(1.03, 7.35)	1.01 (0.5)	0.04*
Time[b]	1.27	(1.17, 1.39)	0.24 (0.05)	<.0001*
Age, years[c]	1.03	(0.98, 1.07)	0.03 (0.02)	0.26
Gender	4.34	(1.33, 14.2)	1.47 (0.6)	0.02*
Study Site[d]	6.23	(1.5, 25.77)	1.83 (0.72)	0.02*

Abbreviations: CI = confidence interval, SE= standard error TB = Tuberculosis, HIV = Human Immunodeficiency Virus, AG = aminoglycoside, *Significant Estimate

[a] Sample consists of the first observation for each two week interval for each subject

[b] Defined as time from admission in two week periods

[c] Age at admission

[d] Study Site 1 is the UTHSCT, study site 2 is TCID/AGHH combined; Site 2 is the reference value

FIGURES

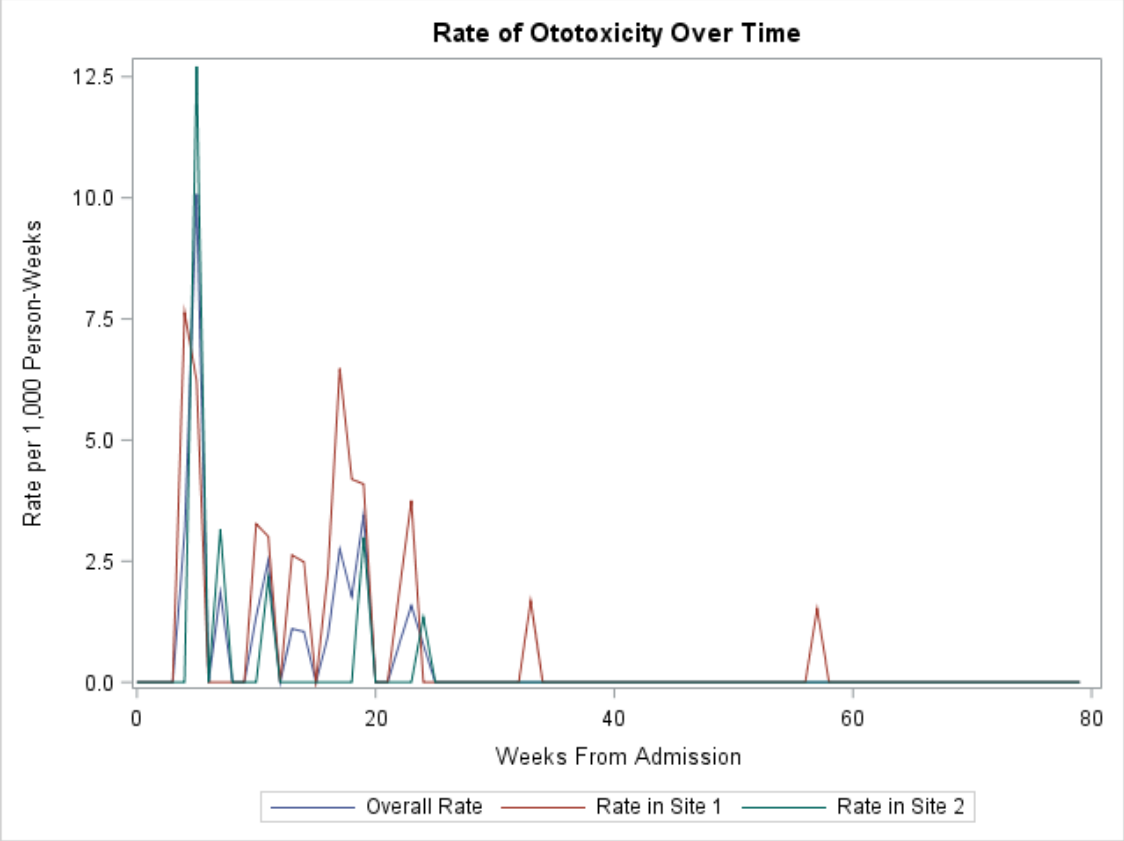

Figure 1a. Rate of Ototoxicity Over Time Among 81 Patients with Therapeutic Drug Monitoring for Tuberculosis and at least 2 Audiograms During Hospital Admission for TB Disease, 1985-2015. Site 1 = UTHSCT, Site 2 = TCID/AGHH. Time from admission was defined as weeks from hospital admission. Ototoxicity was defined as at least a 20 dB increase at any one frequency, 10 dB at two adjacent frequencies or an audiogram at 4 months after start of aminoglycoside treatment or later and at least one frequency greater than 40 dB.

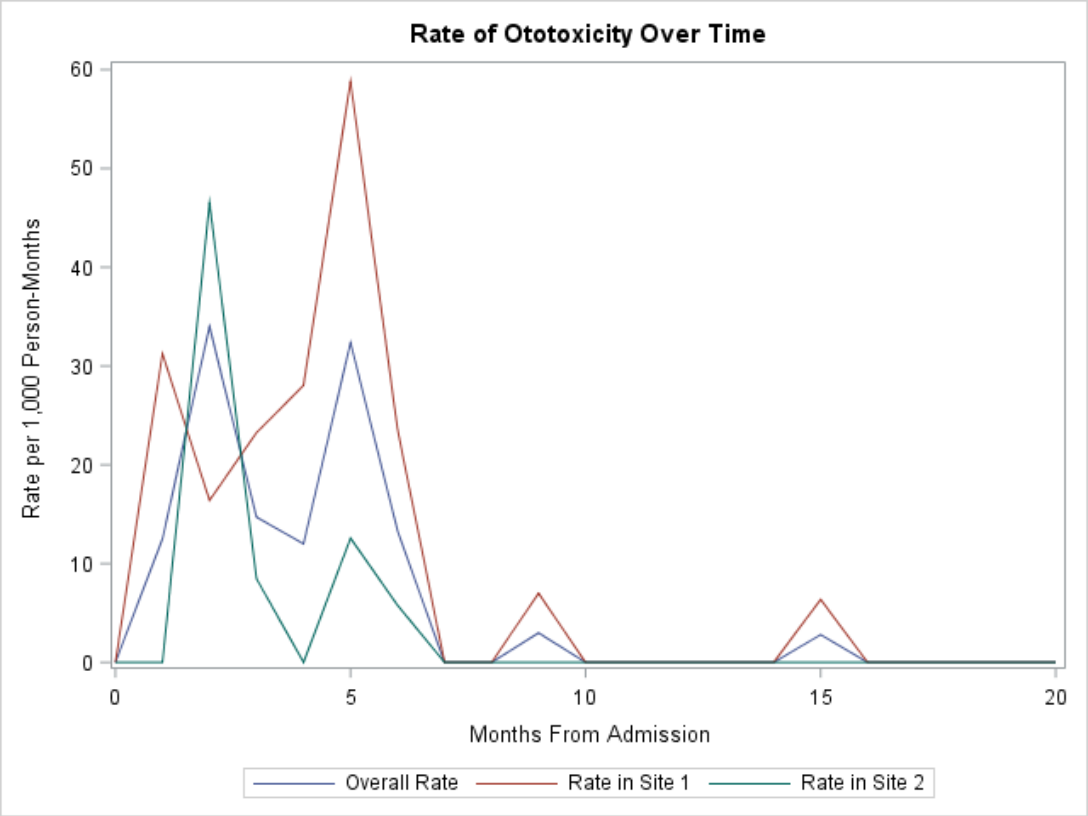

Figure 1b. Rate of Ototoxicity Over Time Among 81 Patients with Therapeutic Drug Monitoring for Tuberculosis and at least 2 Audiograms During Hospital Admission for TB Disease, 1985-2015. Site 1 = UTHSCT, Site 2 = TCID/AGHH. Time from admission was defined as months from admission. Ototoxicity was defined as at least a 20 dB increase at any one frequency, 10 dB at two adjacent frequencies or an audiogram at 4 months after start of aminoglycoside treatment or later and at least one frequency greater than 40 dB.

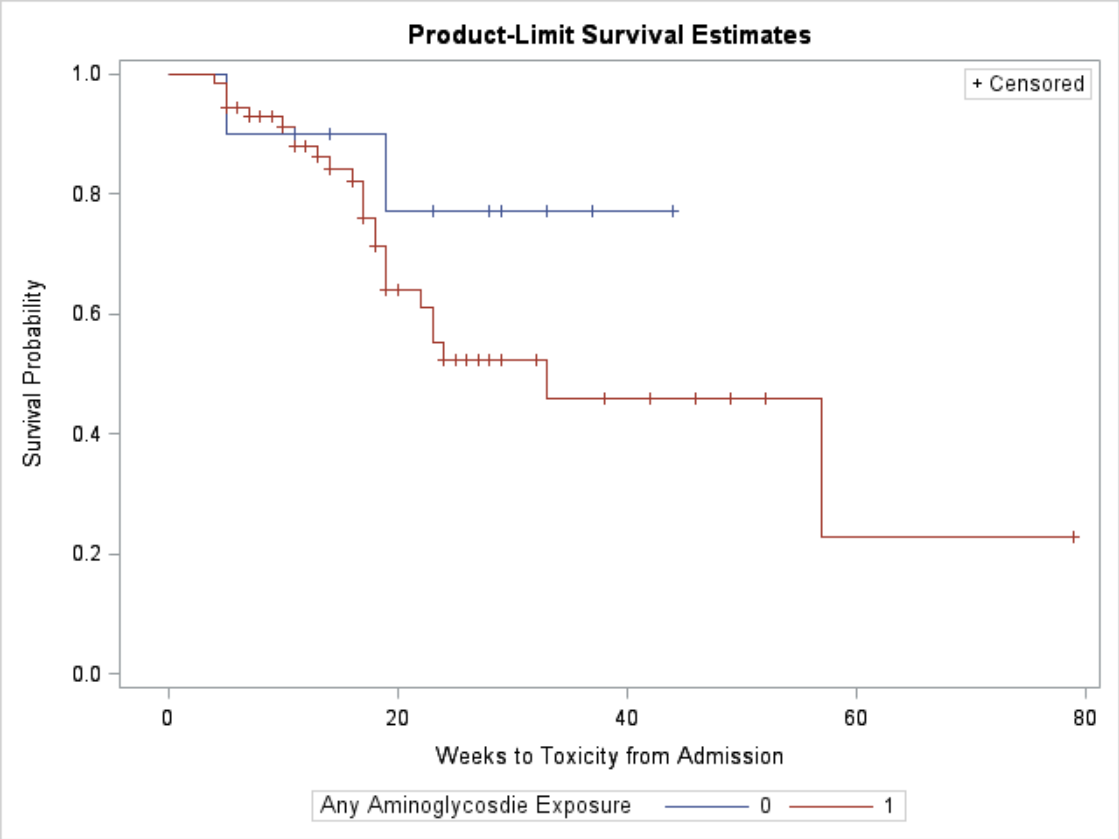

Figure 2a. Survival Curves of Ototoxicity Among 81 Patients with Therapeutic Drug Monitoring for Tuberculosis and at least 2 Audiograms During Hospital Admission for TB Disease, 1985-2015. Ototoxicity was defined as at least a 20 dB increase at any one frequency, 10 dB at two adjacent frequencies or an audiogram at 4 months after start of aminoglycoside treatment or later and at least one frequency greater than 40 dB. Patients were censored on discharge. The curves are not significantly different($\chi^2 = 1.55$, p =0.21).

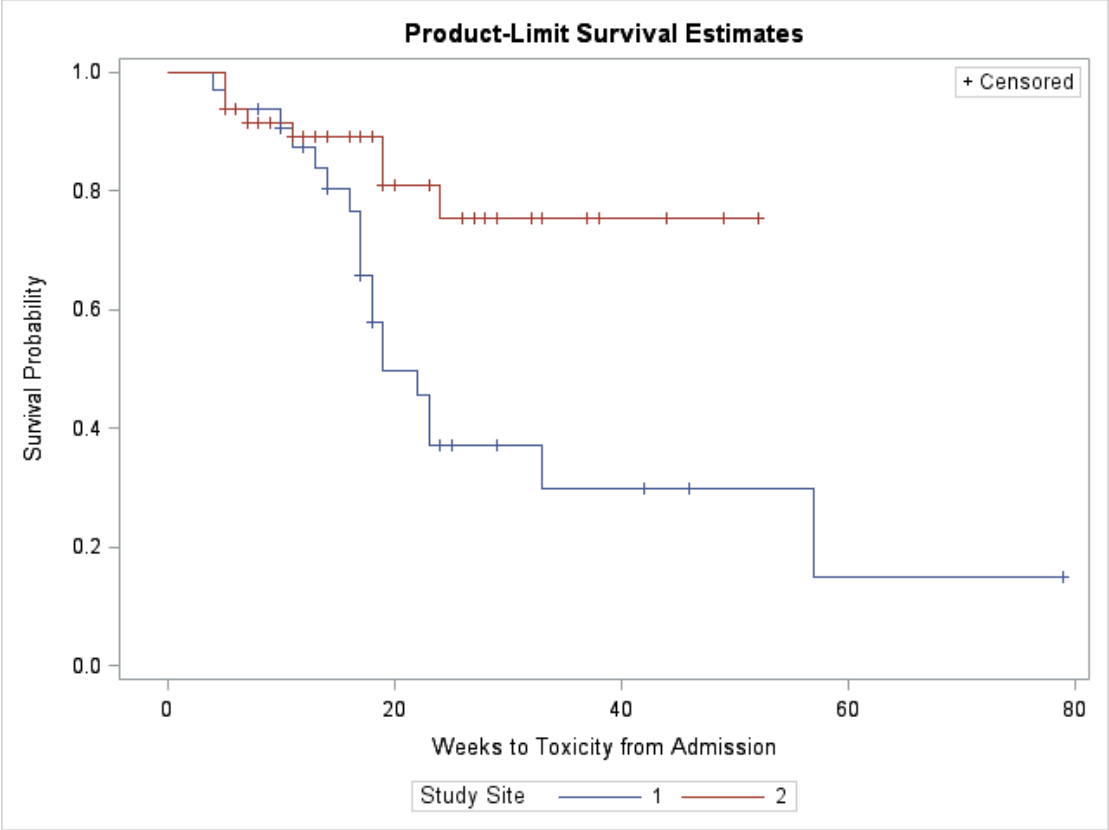

Figure 2b. Survival Curves of Ototoxicity by Study Site Among 81 Patients with Therapeutic Drug Monitoring for Tuberculosis and at least 2 Audiograms During Hospital Admission for TB Disease, 1985-2015. Study site 1 = UTHSCT and 2 = TCID/AGHH. Ototoxicity was defined as at least a 20 dB increase at any one frequency, 10 dB at two adjacent frequencies or an audiogram at 4 months after start of aminoglycoside treatment or later and at least one frequency greater than 40 dB. Patients were censored on discharge. The curves are significantly different ($\chi^2 = 8.33$, $p = 0.003$).

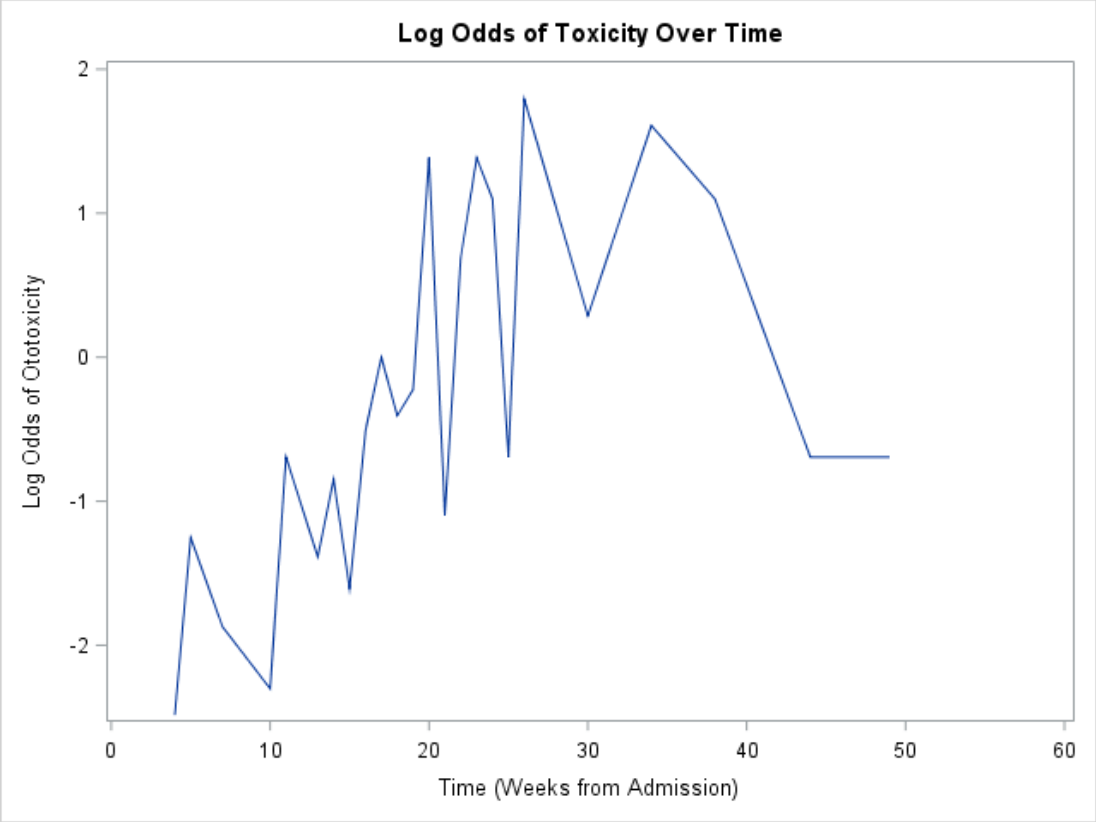

Figure 3a. Log-Odds of Ototoxicity Over Time Among 81 Patients with Therapeutic Drug Monitoring for Tuberculosis and at least 2 Audiograms During Hospital Admission for TB Disease, 1985-2015. Ototoxicity was defined as at least a 20 dB increase at any one frequency, 10 dB at two adjacent frequencies or an audiogram at 4 months after start of aminoglycoside treatment or later and at least one frequency greater than 40 dB. Time was defined as weeks from admission and truncated to 60 weeks or less for easier visual examination.

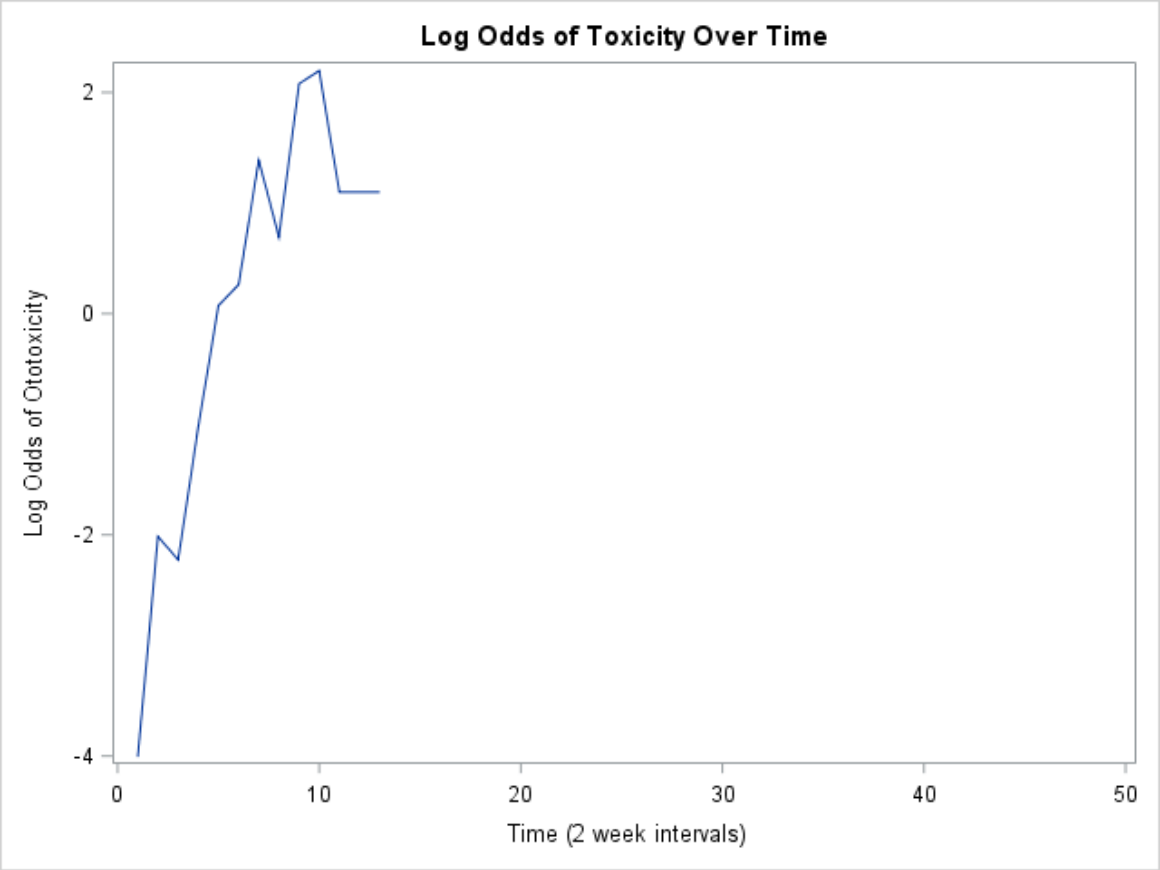

Figure 3b. Log-Odds of Ototoxicity Over Time Among 81 Patients with Therapeutic Drug Monitoring for Tuberculosis and at least 2 Audiograms During Hospital Admission for TB Disease, 1985-2015. Time indicates time from hospital admission in 2-week intervals. Ototoxicity was defined as at least a 20 dB increase at any one frequency, 10 dB at two adjacent frequencies or an audiogram at 4 months after start of aminoglycoside treatment or later and at least one frequency greater than 40 dB. Time was defined as months from admission.

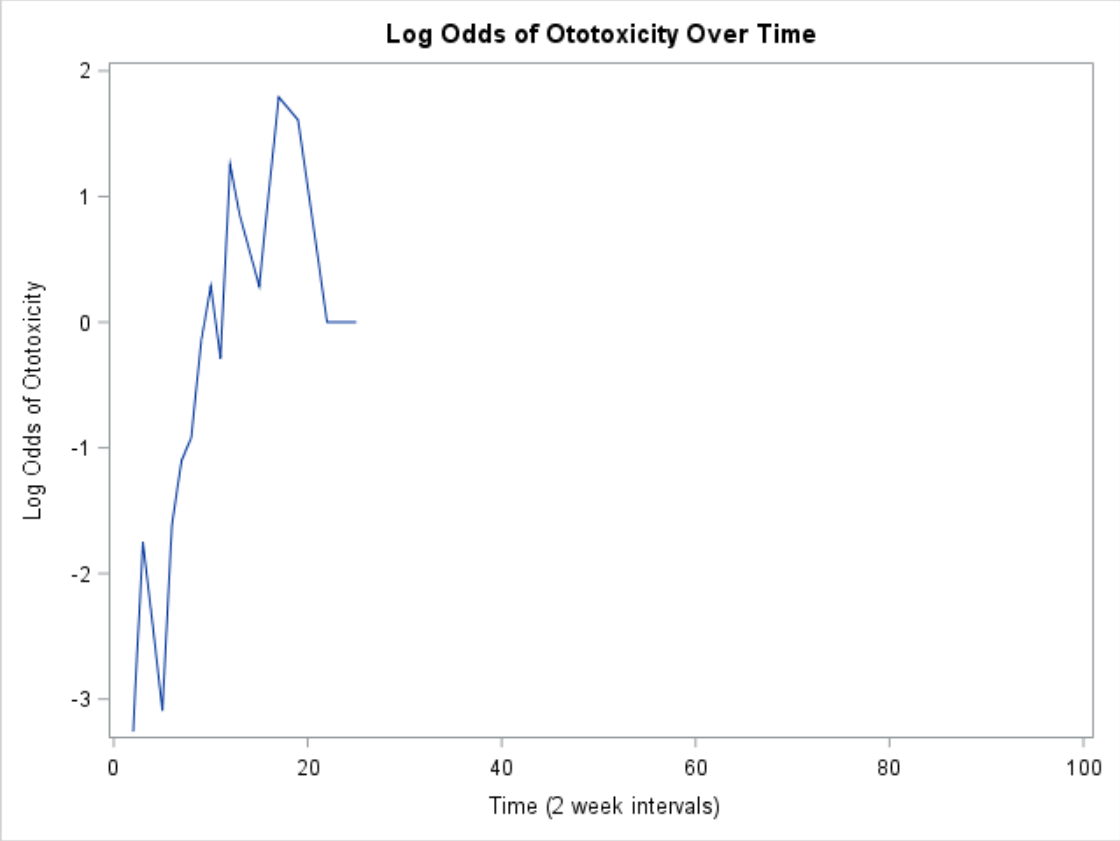

Figure 3c. Log-Odds of Ototoxicity Over Time Among 81 Patients with Therapeutic Drug Monitoring for Tuberculosis and at least 2 Audiograms During Admission, 1985-2015. Ototoxicity was defined as at least a 20 dB increase at any one frequency, 10 dB at two adjacent frequencies or an audiogram at 4 months after start of aminoglycoside treatment or later and at least one frequency greater than 40 dB. Time was defined as 2 week intervals from admission.