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Appropriate Clinical Monitoring as Prevention Against Untoward Side Effects of Prolonged Aminoglycoside Treatment in Patients Treated for Tuberculosis

By

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Master of Public Health

Epidemiology

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Appropriate Clinical Monitoring as Prevention Against Untoward Side Effects of Prolonged Aminoglycoside Treatment in Patients Treated for Tuberculosis

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2010

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An abstract of

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Abstract

Appropriate Clinical Monitoring as Prevention Against Untoward Side Effects of Prolonged Aminoglycoside Treatment in Patients Treated for Tuberculosis

By Amber Choquette Deutschle

Background: The author examined the association between better clinical monitoring and the development of aminoglycoside toxicity among patients who received aminoglycosides as treatment for drug-resistant tuberculosis in a retrospective cohort study. Original data were obtained via chart abstraction for patients admitted to the tuberculosis unit of the University of Texas Health Science Center in Tyler, TX between 1985 and 2010. The toxicities of interest were ototoxicity (measured by serial audiometry) and nephrotoxicity (measured by serial serum creatinine determinations).

Methods: Multivariate logistic regression was used to examine the effect of increased frequency of clinical monitoring on decreasing toxicity. Count of total audiograms and serum chemistries and total regimen changes were used as proxies for clinical monitoring. Stratified analysis, likelihood ratio test, and backward elimination methods were used to examine effect modification by risk factors previously established in literature, using corresponding interaction terms, while change-in-estimate was used to assess confounding.

Results: In total, 541 observations within the original dataset were treated with aminoglycosides; 420 had information on nephrotoxicity development, and 93 had information on ototoxicity development. Forty-four percent of the ototoxicity dataset (n=93) developed ototoxicity (P=0.254) while 23 % of the nephrotoxicity dataset (n=420) developed nephrotoxicity (P<0.0001). Multivariate logistic regression showed significant associations between both aminoglycoside toxicities; ototoxicity and audiogram frequency (crude OR 1.35, 95% CI 1.16,1.58), and nephrotoxicity with creatinine measurement frequency and regimen change frequency (crude OR 1.41, 95% CI 1.29,1.54).

Conclusion: While odds ratios were not in the expected direction, they do not completely contradict the original hypothesis due to use of the proxy variables and lack of a time component. Attending physicians might have noticed developing toxicities and ordered more toxicity measurements and dose changes to manage them rather than ordering more of these prior to the development of the toxicities.

MeSH: aminoglycosides, audiometry, creatinine, hearing loss, nephrotoxicity, ototoxicity, resistant tuberculosis, tuberculosis

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INTRODUCTION

Tuberculosis has reached various epidemic proportions dating back to the first millennium (1). Streptomycin (an aminoglycoside) was proven in the 1947 to be the first clinically effective drug for the treatment of tuberculosis (2). This newly discovered medication led to decreased mortality from fatal forms of tuberculosis and added to the decline of sanitorium use for tuberculosis patients (3). However less than a year following the discovery of streptomycin, reports revealed permanent hearing loss as a common unintended consequence of streptomycin (4). In the 1970's, diminished renal function was found to be another common unintentional consequence of aminoglycoside treatment (5). Although different aminoglycosides have shown various levels of toxicity, all have in some way led to similarly unfortunate side effects (5). The mechanisms by which Aminoglycosides act as antibacterial agents involve inhibiting protein synthesis during bacterial RNA translation (6,7). When administered intravenously or intramuscularly, Aminoglycosides accumulate in the hair cells of the inner ear as well as the renal tubular cells of the kidneys causing cell death leading to ototoxicity and nephrotoxicity (6). Aminoglycosides remain an important second line drug in treatment regimens for multidrug-resistant tuberculosis (MDR-TB) (6). Several studies have investigated the toxicities associated with aminoglycosides, and all point to the need for further investigation into these toxicities (8-17).

In 2014, Tuberculosis (TB) was tied with HIV as the leading infectious disease cause of death worldwide (18). In the same year, 480,000 cases were estimated to be multidrug resistant TB (18). Various studies across the globe show an average incidence of ototoxicity around 27% (ranging between 2% to 70%) and average nephrotoxicity

around 8% (ranging between 0.7% to 15%) in patients treated with aminoglycosides for multidrug resistant tuberculosis (8-17). In these studies, variables considered for significant association with *nephrotoxicity* included gender, age, treatment duration, cumulative dose, dose frequency, dosage size, serum creatinine levels, and prior aminoglycoside use (8-10). Multiple studies found statistically insignificant relationships with all the above variables; however, two studies found statistical significance for larger cumulative dose and longer treatment duration ($P \leq .0.04$) (8, 9). Kanamycin was also noted to be least nephrotoxic compared to amikacin and streptomycin ($P \leq .0.04$) (10). Variables considered for association with *ototoxicity* included gender, age, treatment duration, cumulative dose, serum concentration, dosage size, dosage frequency, prior aminoglycoside use, BMI, history of ototoxicity, drug abuse, smoking history, socioeconomic status, and comorbidities (8-17). Streptomycin was noted to be least ototoxic compared to amikacin and kanamycin ($P \leq 0.03$) (10). Results were contradictory due to several studies claiming statistical significance for certain variables with ototoxicity while other studies claimed insignificance for the same values (8-17). It is of note however, that comparing studies based on significant findings is not entirely reliable due to significance being affected strongly by sample size. The difference in significant findings for these studies rather shows several studies had the power to claim no association for potential predictors while others did not.

After reviewing these study results and researching the mechanisms behind ototoxicity and nephrotoxity, the need for further information regarding the role of these associations remains a priority. However, the studies share a commonality in that variables connected to the wellbeing of these patients are often included in analysis.

These variables included older age, male gender, lower economic status and co morbidities such as diabetes and hypertension (17). Product information for aminoglycosides warns physicians to appropriately monitor patients while on aminoglycosides to prevent toxicities (19). Although various associations to aminoglycoside toxicity remain inconsistent, one recommendation stands out; clinical staff should closely monitor their patients to avoid untoward effects of aminoglycosides. The investigator's hypothesis is that greater frequency of monitoring toxicity (audiograms and creatinine measures) and regimen changes will lead to a decreased odds of developing aminoglycoside toxicities.

MATERIALS AND METHODS

Data

The data for this retrospective cohort study was abstracted via medical chart review of patients admitted to the Tuberculosis Unit of the University of Texas Health Science Center in Tyler, TX (UTHSCT) between 1985 and 2010. During this period, approximately 3000 patients were admitted to the hospital. One hundred percent of patients who had: a) drug-resistant tuberculosis, 2) HIV infection, or 3) therapeutic drug monitoring were compiled into the dataset. In addition, a 25% simple random sample of the other, uncomplicated tuberculosis cases was added. This sample consists of 961 patients and 1093 hospital admissions. As this study is a secondary analysis on a de-identified data set, IRB approval was not required, however an exemption letter was requested and received from the Emory institutional review board. The primary study was approved by UTHSCT and CDC IRBs.

Statistical Analysis

All data analysis was performed using Statistical Analysis Software 9.4 (SAS). Significance of proportions was tested using the student's T test for continuous variables while χ^2 and fisher's exact test were used for categorical variables. The odds of developing nephrotoxicity and ototoxicity were evaluated among this cohort comparing different levels of monitoring, while also examining other known risk factors and demographics. One primary outcome of interest was ototoxicity, defined as any single decrease in hearing threshold of 20 dB or any 2 decreases of 10 dB at any point during hospital admissions. The second primary outcome of interest was nephrotoxicity, defined as any increase $\geq$ 0.3 mg/dl for this analysis. Previous studies have defined

nephrotoxicity as any increase in serum creatinine ≥ 0.5 mg/dl (8, 9, 12). However, to obtain more sensitive results for a smaller sample size, nephrotoxicity criteria was lowered to ≥ 0.3 mg/dl for this particularly analysis. Both outcome definitions were based on other literature examining the effect of aminoglycosides on nephrotoxicity and ototoxicity (8-10, 12, 15, 16). The exposures of interest were calculated by looking at two continuous variables corresponding to each of the outcome variables. For nephrotoxicity, the total count of serum chemistry measurements and total dosing regimen changes were used to assess the relationship of clinical monitoring on decreased serum creatinine. For ototoxicity, the total count of audiogram measures and total dosing regimen changes were likewise used to assess the relationship of clinical monitoring and decreased hearing thresholds. Frequency count of audiograms and serum creatinine measures were based on how many days during a patient's admission a patient was provided at least one measurement. Total dosing regimen changes included anytime the tuberculosis treatment medication was changed including dose, frequency, and actual drug type changes (including more than just aminoglycosides).

As the abstracted data existed in several related tables, the data were cleaned, merged, and cleaned again to create the final dataset for analysis. Descriptive statistics were obtained for all variables of interest (gender, age, cumulative dose, treatment duration, etc.) as displayed in **Tables 1** through **Tables 4**. Potential effect modifiers and confounders were examined to determine cut points most meaningfully related to the main variables of this analysis. Continuous variables were evaluated to ensure they followed a linear relationship with the logit of the outcomes. Two modeling strategy methods were considered; the first including assessment for effect modification,

confounding, exposure assessment, and goodness of fit statistics. The second included all previously mentioned assessments excluding effect modification. Effect modification was assessed using log-likelihood ratio tests followed by backward elimination. Confounding was assessed by looking at change in estimate of effect measure for each potential confounder following interaction assessment; any models with effect change greater than 10% of the gold standard model were used for final model consideration. Exposure assessment was performed by looking at the odds ratio of each exposure given the presence of the other in the model, the joint effect of both exposures as well as the effect of each exposure when the other exposure was removed from the model. Goodness of fit statistics included the Hosmer-Lemeshow test of fit as well as receiver operating characteristic curves (ROC) for model discrimination.

Potential confounders were considered based primarily on previous literature followed by association of each literature-derived variable to outcome and exposure. Results for the association between clinical monitoring and development of both aminoglycoside toxicities were expressed as odds ratios (OR) with 95% confidence intervals. Both the nephrotoxicity and ototoxicity models were analyzed at 0.05 significance level. Complete case analysis was chosen to address missing data. Due to fluctuating Tuberculosis treatment methods over the 25 years from which this data was collected, the final models were used to compare the first half of the data with the second half of the data to ensure the odds of disease did not vary greatly due to these changing practices.

RESULTS

Univariate descriptive statistics

The cohort of this dataset treated with aminoglycosides during their admission consisted of 541 observations. The cohort included in complete case analysis for the nephrotoxicity models totaled 420 (77.6%) while the cohort included in complete case analysis for the ototoxicity models totaled 93 (17.2%). This specific cohort was made up of 425 (78.70%) males, median age of 45 years (IQR: 34.00, 6.00), and followed a racial distribution of 176 (33.52%) White, 157 (29.90%) Black, 37 (7.05%) Asian and 155 (29.52%) Hispanic individuals. Patients with a current or former prison history totaled 48 (8.87%) and the number of homeless was 80 (16.36%). Median educational achievement was 10 years (IQR: 6.00, 12.00), while unemployed individuals numbered 302 (58.75%). Among those in the cohort with substance abuse history, 90 (17.51%) had a former history of alcohol abuse, 200 (38.91%) had a current problem with alcohol abuse, and 100 (19.88%) had a history of any drug abuse (illicit and iv). Two hundred sixty-two (51.27 %) patients were current smokers while 97 (18.98%) were former smokers. Median pack years among smokers was 30 years (IQR: 20.00, 50.00). The median body mass index among the cohort was 20.00 kg/m^2 (IQR: 18.00, 23.00). One hundred fifty-eight (31.79%) individuals within this dataset were malnourished. The median number of comorbidities per patient was 1.00 (IQR: 0.00, 3.00); which included diabetes, lung disease, renal disease, liver disease, epilepsy, history of stroke, cancer, any psychiatric disorder, cardiac disease, gastrointestinal disease, autoimmune disease, and dementia. Those diagnosed with HIV consisted of 44 individuals (8.68%). The above demographic and clinical characteristics of this cohort may also be found in **Table 1**.

Additional characteristics related to aminoglycoside dosages were collected and can be found in **Table 2**. This cohort was treated with 4 different types of aminoglycosides; AMK/KAN (amikacin and kanamycin) was given to 146 (28.02%) individuals, CAP (capreomycin) to 236 (45.30%) individuals and STM (streptomycin) to 336 (64.49%) individuals. The percentages overlap due the non-mutually exclusiveness of aminoglycoside treatment during the admission period. Median aminoglycoside treatment duration was 110.00 days (IQR: 46.00, 248.00) while the median cumulative dose was found to be 63.00 grams (IQR: 27.64, 136.28). The median of total aminoglycoside changes numbered 3.00 (IQR: 2.00, 5.00) while the median daily dose was found to be 0.44 mg/dl (IQR: 0.33-0.50). Ninety-two (17.01%) patients had prior exposure to aminoglycosides with their prior cumulative dose median at 103.43 g (IQR: 58.00-283.50).

Variables related to the outcomes (nephrotoxicity and ototoxicity) and exposures can be found in **Table 3** and **Table 4**. One hundred patients (23.81%) of the population with serum creatinine data were found to have experienced nephrotoxicity. Of the patients with multiple audiograms, 41 (44.09%) experienced ototoxicity. The median for audiogram measurements per patient was 2.00 (IQR: 1.00, 5.00), and the total count of creatinine measurements median 6.00 (IQR: 3.50, 12.00) per patient. Median total count of dosing regimen changes equaled 10.00 (IQR: 6.00, 14.00) per patient.

Bivariate analysis

Upon literature review, 26 variables were considered as potential confounders. Logistic regression for single exposure models was used as a screening method to determine which of these should be considered as potential confounders or effect

modifiers. The count of comorbidities per patient, prior exposure to aminoglycosides, aminoglycoside dose administration (weekly vs. intermittent), homelessness, prison history, as well as capreomycin treatment were found to be potential effect modifiers between ototoxicity and the dual exposures of audiogram frequency and dose change frequency. Potential confounders for ototoxicity and clinical care exposures included smoking pack years and prior aminoglycoside cumulative dose.

Age, BMI, count of comorbidities per observation, average daily dose during admission, previous aminoglycoside cumulative dose, malnutrition, aminoglycoside types capreomycin & streptomycin, and prior exposure to aminoglycosides were potential effect modifiers for the associations of creatinine frequency and dose change frequency with nephrotoxicity. The only potential confounder for the nephrotoxity models were prior aminoglycoside dose. However, all three noted potential confounders for both toxicity type models were found to either have too small stratified sample sizes or caused model separation and were subsequently removed from modeling strategy.

Multivariate logistic regression analysis

Upon completion of modeling strategy, interaction was deemed to not be pertinent to the overall relationship between the exposures and outcomes due to lack of significance within the likelihood ratio test and unnecessarily complicated multi-interaction models. Modeling strategy determined that both these toxicity exposure relationships were best described by the crude model (exposures only). Further, while both exposures were deemed necessary following exposure assessment for nephrotoxicity, audiogram frequency was the only significant exposure for the ototoxicity model. For every additional audiogram performed per patient during their hospital

admission, the odds of experiencing ototoxicity significantly increased by 1.35 (95% CI 1.16,1.58). For every additional measurement of serum creatinine, the odds of nephrotoxicity significantly increased by 1.3. while for every additional change in tuberculosis treatment medications (inclusive of all drug type), the odds of nephrotoxicity significantly increased by 1.08. When these exposures are accounted for together, a multiplicative effect ensues and for every combined one-unit increase of both these exposures, the odds of nephrotoxicity increased by 1.4 (crude OR 1.41, 95% CI 1.29,1.54).

DISCUSSION

As tuberculosis remains one of the leading causes of death worldwide, those with drug-resistant tuberculosis remain an important cohort needing treatment (18). One of the most common treatment regimens for drug-resistant tuberculosis include aminoglycosides (5). While aminoglycosides are effective, they sometimes come at a cost causing various toxicities such as ototoxicity and nephrotoxicity (5).

Prior studies around the world have attempted to understand various risk factors and their associations with aminoglycoside toxicities; those reviewed for this study included populations from Colorado, the Netherlands, Turkey, Latvia, Russia, Iran, as well as several countries in Africa (8-17). These studies were mostly retrospective (several were prospective and involved randomization) review of patients admitted either to hospitals or respiratory units within the hospitals (8-17). With sample sizes ranging from 87 to 1027, this analysis looking at clinical care falls right in the middle with a sample size of 541 (8-17). However, this clinical care analysis looks at data for a much longer period, 25 years (8-17). These studies attempted to understand risk factors associated with aminoglycoside toxicity, however many were contradictory in their findings; either finding no association or in conflict with the findings of other studies.

This analysis utilized a retrospective cohort design to discover if better clinical care is associated with less incidence of aminoglycoside toxicities to better understand prevention methods beyond risk factors. "Better clinical care" was defined by the frequency of monitoring for toxicities and the frequency of changing tuberculosis treatment. Thus, the variables best suited to represent clinical care were the joint effect of dose and medication changes and specific toxicities measurement counts (audiograms

for ototoxicity and creatinine measurements for nephrotoxicity). For every additional measurement of serum creatinine combined with every additional change in tuberculosis treatment (inclusive of all drug type), the odds of nephrotoxicity significantly increased by 1.41 (95% CI 1.29,1.54); see **Table 5**. As treatment change was not a significant contributor to this double exposure model for ototoxicity, only audiogram frequency was used to describe clinical care. For every additional audiogram performed per patient during their hospital admission, the odds of experiencing ototoxicity significantly increased by 1.35 (95% CI 1.16,1.58); see **Table 5**.

Initially, the hypothesis was that both odds ratios would show a negative relationship; more toxicity specific measurements and more dosing regimen changes would lead to decreased odds of developing aminoglycoside toxicities. However, the positive relationship does not necessarily contradict the idea that better clinical care has an opposite effect on developing toxicities; the element that could be missing from this analysis is time. It is possible that as a patient showed signs of developing aminoglycoside toxicities, a doctor increased measures and changed regimens to counteract the toxic side effects.

The sampling method for this dataset also plays a potential detriment to revealing the true analysis of aminoglycoside toxicity and better clinical care. The sampling method to collect this dataset was not a simple random sample, but rather a stratified sample collecting 100% of patients with drug-resistant tuberculosis, HIV infection, or therapeutic drug monitoring, as well as a 25% simple random sample of the other, uncomplicated tuberculosis cases. It is also possible the restriction to analyze patients who received aminoglycoside counteracted the potential bias introduced with this

sampling strategy. Further investigation using software (such as SUDAAN) that might be able to account for the sampling scheme of the dataset might provide better insight on the exposure outcome relationship.

Strengths

One strength of this study is the fact the hospital from which this dataset was pulled was resource rich compared to global locations were resources are limited. The earlier data in this set was collected at a time when nearly all tuberculosis patients were admitted to the hospital, so a wider collection of tuberculosis patients was made part of this dataset. This time difference in treatment protocol also potentially posed as a problem by not being accurately reflected the overall association found in this study. To ensure this was not the case, the final models were used to compare the associations found in the first half of the dataset (1985-1998) with the second half of the dataset (1998-2010). The results were not drastically different between the two-time frames, as demonstrated in **Table 5**, so this remained a strength. The large size of this data set also represents a strength because any type of results found will be far more meaningful, especially if significantly pronounced. As this data was collected from medical charts, standardized chart review was reliable and serves as another strength.

Limitations

The biggest limitation to this study is missing data. All variables and measurements were recorded for patients who received actual care as opposed to being enrolled in a clinical trial. Hence, the recorded data were not always complete.
One primary example of missing data that potentially caused the biggest detriment to this analysis were the number of missing audiograms. To measure hearing loss, at least two

audiograms are necessary. Only 139 of the 541 patients being treated with aminoglycosides had a least one audiogram. Forty-six of these only had 1 audiogram; leaving around 80% of patients receiving ototoxic drugs without any form of hearing loss monitoring. Studies have shown patients have poor self-reporting practices regarding hearing loss in a hospital setting, so this not only shows a limitation within this dataset, but also a limitation for the care of these patients (20). However, for the total missing data, analysis was run with the number of observations that had complete information for all variables within the final models (complete case analysis). Since the final models were crude, limited information was lost. Another limitation is the possibility of imprecise measurements as data was collected in a busy hospital setting. A third limitation is the possible lack of generalizability. This study was performed using data from an inpatient unit in one city in Texas, where demographics and characteristics might differ in a different state let alone across the world.

Future directions and public health importance

As tuberculosis remains one of the top global killers, maintaining treatment that ensures avoidance of unnecessary aminoglycoside toxicities remains a priority. The relationship between these toxicities and quality clinical care could be better defined by future studies looking at multiple dataset types and sources around the world. Another benefit would be analyzing which commonly recorded variables best reflect clinical care.

Conclusion

This analysis has hopefully added to prevention methods against aminoglycoside toxicities. Although this data primarily came from a small section of Texas, and hence could lack generalizability to the population treated with aminoglycosides, the resource

rich environment could shed light on measurements which global sites might not have access to.

Clinical care, as demonstrated by count of toxicity related measures as well as dose regimen changes, was significantly related to the development of aminoglycoside toxicity in the crude form model. Future research would best contribute to this analysis by considering the reliability of these proxy variables as descriptors of clinical care. Discovering practical methods to prevent aminoglycoside toxicities will ensure patients are not being saved from drug-resistant tuberculosis only to be provided a decreased quality of life via their treatment.

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Tables

Table 1. Socio Demographic Characteristics of 541 Patients Treated with Aminoglycosides for Persistent Tuberculosis in Tyler, TX; 1985 - 2008

		Overall		Ototoxicity (n = 93)				Nephrotoxicity (n= 420)		
Characteristics [a]		n	(n=541)	n	Cases (n=41)	n	Controls (n=52)	n	Cases (n=100)	n	Controls (n=320)
Age [b]		539	**45.00 (34.00, 56.00)**	41	**46.00 (34.00, 55.00)**	52	**41.00 (35.50, 52.50)**	100	**50.00 (38.00, 62.00)**	319	**43.00 (33.00, 54.00) *****
Sex:	Male	540	425 (78.70)	41	33 (80.49)	52	34 (65.38)	99	83 (83.84)	320	252 (78.75)
Race		525		38		51		98		309	
	White		176 (33.52)		12 (31.58)		15 (29.41)		31 (31.63)		100 (32.36)
	Black		157 (29.90)		6 (15.79)		6 (11.76)		31 (31.63)		91 (29.45)
	Asian		37 (7.05)		3 (7.89)		6 (11.76)		6 (6.12)		24 (7.77)
	Hispanic		155 (29.52)		17 (44.74)		24 (47.06)		30 (30.61)		94 (30.42)
Prison History: Current/Former		541	48 (8.87)	41	1 (2.44)	52	4 (7.69)	100	7 (7.00)	320	31 (9.69)
Homeless		489	80 (16.36)	36	4 (11.11)	46	6 (13.04)	92	16 (17.39)	286	52 (18.18)
Education [b]		467	**10.00 (6.00, 12.00)**	34	**9.00 (5.00, 11.00)**	43	**10.00 (6.00, 12.00)**	85	**10.00 (6.00, 12.00)**	275	**10.00 (6.00, 12.00)**
Unemployed		514	302 (58.75)	40	28 (70.00)	52	34 (65.38)	94	56 (59.57)	302	185 (61.26)
Alcohol Abuse		514		41		49		96		304	
	Former		90 (17.51)		6 (14.63)		8 (16.33)		19 (19.79)		47 (15.46)
	Current		200 (38.91)		17 (41.46)		16 (32.65)		28 (29.17)		128 (42.11)
Smoker		511		39		51		95		303	
	Former		97 (18.98)		8 (20.51)		10 (19.61)		22 (23.16)		56 (18.48)
	Current		262 (51.27)		16 (41.03)		24 (47.06)		44 (46.32)		161 (53.14)

Pack Years	150	**30.00 (20.00, 50.00)**	7	**50.00 (27.00, 50.00)**	12	**33.50 (12.50, 57.50)**	17	**40.00 (18.00, 60.00)**	92	**30.00 (16.50, 50.00)**
Any HX of Drug Abuse [c]	503	100 (19.88)	40	6 (15.00)	50	10 (20.00)	89	13 (14.61)	302	65 (21.52)
BMI	491	**20.00 (18.00, 23.00)**	37	**20.00 (19.00, 23.00)**	46	**20.00 (18.00, 22.00)**	91	**20.00 (18.00, 24.00)**	288	**20.00 (17.00, 23.00)**
Malnutrition	497	158 (31.79)	38	12 (31.58)	48	15 (31.25)	93	32 (34.41)	293	102 (34.81)
HIV Diagnosis	507	44 (8.68)	40	2 (5.00)	50	3 (6.00)	94	7 (7.45)	304	29 (9.54)
Comorbidity [d]	541	**1.00 (0.00, 3.00)**	41	**3.00 (1.00, 4.00)**	52	**2.50 (1.00, 4.00)**	100	**2.00 (1.00, 4.00)**	320	**1.00 (0.00, 3.00)****
Any		348 (64.33)		32 (78.05)		41 (78.85)		80 (80.00)		202 (63.13)**

BMI: Body Mass Index, HX: History,

*** Indicates P < .0001 for comparison with toxicity cases, by t-test for continuous variables and exact Fisher's and chi 2 for categorical variables

** Indicates P < .01 for comparison with toxicity cases, by t-test for continuous variables and exact Fisher's and chi 2 for categorical variables

[a] Bold values to the left represent Median (interquartile Range), while non, italics to the right of the cell represent N (%)

[b] *Unit: Years*

[c] *Includes illicit and intravenous drug abuse*

[d] *Median dealing with the sum of: Diabetes, Any Lung Disease, Renal Disease, Liver, Epilepsy, Stroke, Cancer, Psychiatric disorder, Cardiac, Gastric Disease, Autoimmune disease, & Dementia*

Table 2. Aminoglycoside Characteristics of 541 Patients Treated with Aminoglycosides for Persistent Tuberculosis in Tyler, Texas; 1985 through 2008

		Overall		Ototoxicity (n = 93)				Nephrotoxicity (n= 420)		
Characteristics [a]	n	(n=541)	n	Cases (n=41)	n	Controls (n=52)	n	Cases (n=100)	n	Controls (n=320)
AG Type [b]	541		93		52		100		310	
AMK/KAN		146 (28.02)		19 (46.34)		23 (44.23)		37 (37)		87 (28.06)
CAP		236 (45.30)		31 (75.61)		34 (65.38)		59 (59)		126 (40.65) **
STM		336 (64.49)		17 (41.46)		27 (51.92)		52 (52)		222 (71.61) **
Treatment Duration [c]	467	**110.00 (46.00, 248.00)**	38	**440.00 (142.00, 1059.00)**	49	**212.00 (88.00, 637.00)**	96	**124.00 (62.00, 413.50)**	280	**109.50 (46.00,237.50) ****
Cumulative Dose[d]	437	**63.00 (27.64, 136.28)**	38	**171.75 (88.86, 351.52)**	48	**78.16 (38.80, 258.04)**	89	**93.00 (36.00, 179.00)**	265	**58.12 (30.00, 132.00)**
Total AG Changes	521	**3.00 (2.00, 5.00)**	41	**4.00 (3.00, 9.00)**	52	**4.00 (3.00, 7.50)**	100	**4.00 (2.00, 800)**	310	**3.00 (2.00, 4.00) *****
Daily Dose (mg/dl)	509	**0.44 (0.33, 0.50)**	41	**0.38 (0.33, 0.50)**	51	**0.38 (0.33, 0.50)**	98	**0.43 (0.33, 0.50)**	305	**0.46 (0.36, 0.50)**
Daily		10 (1.96)		40 (97.56)		0 (0)		4 (4.08)		5 (1.64)
Weekly vs. Intermittent		499 (98.04)		1 (2.44)		51 (100)		94 (95.92)		300 (98.36)
Prior AG Exposure	541	92 (17.01)	41	5 (12.20)	52	6 (11.54)	100	10 (10)	320	54 (16.88)
Prior Cumulative Dose [c]	65	**103.43 (58.00, 283.50)**	2	**208.63 (173.25, 244.00)**	3	**161.71 (83.14, 294.29)**	5	**85.14 (61.09, 324.00)**	39	**133.71 (70.71, 283.50)**

AG: Aminoglycosides, AMK: Amikacin, CAP: Capreomycin, KAN: Kanamycin, STM: Streptomycin

*** Indicates P < .0001 for comparison with toxicity cases, by t-test for continuous variables and exact Fisher's and chi 2 for categorical variables

** Indicates P < .01 for comparison with toxicity cases, by t-test for continuous variables and exact Fisher's and chi 2 for categorical variables

[a] Bold value to the left represent Median (interquartile Range), while non-italics to the right of the cell represent N (%)

[b] *Drug treatment types are not mutually exclusive of each other*

[c] *Unit: Days*

[d] *Unit: Grams*

Table 3. Audiometry Related Characteristics of 541 Patients Treated with Aminoglycosides for Persistent Tuberculosis in Tyler, TX; 1985 - 2008

Characteristics [a]	n	Overall (n=541)	n	Ototoxicity (n = 93) Cases (n=41)	n	Controls (n=52)
Ototoxicit[y b]	93	41 (44.09)	41	41 (100)	52	0
Count of Audiogram Measurements	139	**2.00 (1.00, 5.00)**	41	**6.00 (3.00, 11.00)**	52	**3.00 (2.00, 4.00)*****
Count of Dose Regimen Changes	535	**7.00 (5.00, 10.00)**	41	**10.00 (7.00, 17.00)**	52	**9.50 (7.00, 13.00)**
Count of Elevated Ear/Frequency Combos	139[c]	**4.00 (3.00, 6.00)**	41	**4.00 (2.00, 5.00)**	52	**4.00 (3.00, 6.00)**
Count of all per ear frequencies with ≥ 10 dL decrease	93	**1.00 (0.00, 3.00)**	41	**4.00 (2.00, 8.00)**	52	**0.00 (0.00, 1.00)*****
Elevated Audiogram at baseline	139	136 (97.84)	41	40 (97.56)	52	51 (98.08)
Hearing marked as complication	541	12 (2.22)	41	2 (4.88)	52	4 (7.69)
Vestibular marked as complication	541	12 (2.22)	41	4 (9.76)	52	1 (1.92)

*** Indicates P < .0001 for comparison with toxicity cases, by t-test for continuous variables and exact Fisher's and chi 2 for categorical variables

** Indicates P < .01 for comparison with toxicity cases, by t-test for continuous variables and exact Fisher's and chi 2 for categorical variables

[a] Bold value to the left represent Median (interquartile Range), while non, italics to the right of the cell represent N (%)

[b] Defined as any one occurrence of ≥ 20 dB loss or any two ≥ 10 dB loss

[c] 46 Patients only had 1 Audiogram date

Table 4. Serum Creatinine Related Characteristics of 541 Patients Treated with Aminoglycosides for Persistent Tuberculosis in Tyler, TX; 1985 - 2008

		Overall		Nephrotoxicity (n= 420)		
Characteristics [a]	n	(n=541)	n	Cases (n=100)		Controls (n=320)
Nephrotoxicity (≥ 0.5 ml/dg)	420	64 (15.24)	100	64 (64)	320	0***
Nephrotoxicity (≥ 0.3 ml/dg)	420	100 (23.81)	100	100 (100)	320	0***
Count of Creatinine Measurements	536	**3.00 (2.00, 4.00)**	100	**6.00 (3.50, 12.00)**	320	**3.00 (3.00, 4.00) *** **
Count of Dose Regimen Changes	535	**7.00 (5.00, 10.00)**	100	**10.00 (6.00, 14.00)**	318	**7.00 (5.00, 10.00) *** **
Nephrotoxicity marked as a complication	541	18 (3.33)	100	17 (17.00)	320	1 (0.31) ***
Serum Creatinine Levels [b]						
Highest	536	**1.00 (0.80, 1.20)**	100	**1.60 (1.20, 2.30)**	320	**0.90 (0.70, 1.10) *** **
Count Above Upper Limit	536	**0 (0)**	100	**2.00 (0.50, 8.50)**	320	**0 (0) *** **
Any Increase from Baseline	420	**1.00 (0.00, 2.00)**	100	**4.00 (2.00, 10.00)**	320	**0 (0.00, 1.00) *** **
Average Change	410	**0 (-0.05 , 0.05)**	97	**0.04 (0.00, 0.10)**	300	**0 (-0.05, 0.30) *** **
Overall Change	296	**0 (-0.10 , 0.20)**	65	**0.30 (0.20, 0.70)**	176	**0 (-0.10, 0.10) *** **
Serum Creatinine Levels [c]						
Elevated Baseline	538	53 (9.85)	100	10 (10)	320	30 (9.38)
Increase in Average Creatinine levels	410	162 (39.51)	97	71 (73.20)	300	86 (28.67) ***
Average Change Increase ≥ 0.5 ml/dg	410	0 (0)	97	0 (0)	300	0
Average Change Increase ≥ 0.3 ml/dg	410	3 (0.73)	97	3 (3.09)	300	0*
Increase between First and last	296	114 (38.51)	65	60 (92.31)	176	54 (30.68)***
Increase Between First and Last ≥ 0.5 ml/dg	296	27 (9.12)	65	27 (41.54)	176	0***
Increase Between First and Last ≥ 0.3 ml/dg	296	46 (15.54)	35	46 (70.77)	176	0***

*** Indicates P < .0001 for comparison with toxicity cases, by t-test for continuous variables and exact Fisher's and chi 2 for categorical variables

** Indicates P < .01 for comparison with toxicity cases, by t-test for continuous variables and exact Fisher's and chi 2 for categorical variables

* Indicates P < .05 for comparison with toxicity cases, by t-test for continuous variables and exact Fisher's and chi 2 for categorical variables

[a] Bold value to the left represent Median (interquartile Range), while non, italics to the right of the cell represent N (%)

[b] Median per observation

[c] Count per dataset

Table 5. Crude Associations of Study among 541 Patients Treated with Aminoglycosides for Persistent Tuberculosis in Tyler, TX; 1985 - 2008

Outcome	Exposures	Cases/Controls (n)	OR	95% CI	P Value
Overall					
Ototoxicity [a]	Audiogram Frequency	41/52	1.35	1.16, 1.58	0.0001
Nephrotoxicity [b]	Creatinine Frequency	100/320	1.3	1.22, 1.47	<0.0001
Nephrotoxicity [b]	Dose Regimen Change Frequency	100/318	1.0869	1.05, 1.13	<0.0001
Nephrotoxicity [b]	Creatinine Frequency Dose Regimen Change Frequency	100/318 [c]	1.41	1.29, 1.54	<0.0001
Wave 1 [d]					
Ototoxicity [a]	Audiogram Frequency	19/30	1.31	1.05, 1.62	0.0154
Nephrotoxicity [b]	Creatinine Frequency Dose Regimen Change Frequency	63/242	1.53	1.36, 1.73	<0.0001
Waves 2 & 3 [e]					
Ototoxicity [a]	Audiogram Frequency	22/22	1.39	1.11, 1.74	0.0037
Nephrotoxicity [b]	Creatinine Frequency Dose Regimen Change Frequency	37/76	1.24	1.09, 1.40	0.0009

[a] Ototoxicity defined as any one occurrence of ≥ 20 dB loss or any two ≥ 10 dB loss

[b] Nephrotoxicity defined as any increase in serum creatinine levels ≥ 0.3 ml/dg

[c] Two controls were missing information for both exposures

[d] First half of the dataset, patients approximately admitted between 1985-1998

[e] Second half of the dataset, patients approximately admitted between 1998-2010