THE INCIDENCE AND PREDICTORS OF VANCOMYCIN
ASSOCIATED NEPHROTOXICITY

A Thesis in
Public Health Sciences
by
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ABSTRACT

Introduction: Earlier studies have reported a low incidence of vancomycin associated nephrotoxicity, but recent studies are reporting higher incidence that can exceed 30%. To date predictors of nephrotoxicity remain unclear. Data in regard to long treatment courses are very sparse. In this study we aim to better estimate the incidence and evaluate predictors of vancomycin associated nephrotoxicity in a cohort of patients predominated by long treatment courses.

Methods: We conducted a retrospective study on patients who were treated with vancomycin by a tertiary center in mid-Pennsylvania between 01/01/2007 and 07/31/2012. We included adult patients, 18 years of age and older, who are not on dialysis and had a creatinine value below 2 mg/dl both on admission and when vancomycin was started. We identified those who developed nephrotoxicity based on an increase in the serum creatinine level by 0.5 mg/dL or 50% from baseline on at least two consecutive readings while on vancomycin. We then compared the subjects who developed nephrotoxicity and those who did not in regards to vancomycin dosing, trough levels, baseline creatinine, underlying infection, residence in critical care unit, co morbid conditions, concurrent nephrotoxic treatments, and baseline characteristics.

Results: During the study period 579 patients were included. Of those, 154 (26.6%) met the definition of nephrotoxicity, 64 patients (11.1%) met the definition after 14 days of treatment. Though the initial trough level (mg/dl) was significantly associated with nephrotoxicity in the bivariate analysis, this effect was no longer significant after adjusting for other variables. We found that residence in the intensive care unit, concurrent use of
loop diuretics, and co-morbidity with liver cirrhosis are independent risk factors for vancomycin associated nephrotoxicity. We also found that higher baseline creatinine value has protective effects against the development of nephrotoxicity (using a cutoff point of 0.8mg/dl, adjusted OR [95% confidence interval] = 0.40 [0.25-0.66]; adjusted p value = 0.0003).

**Conclusion:** Vancomycin associated nephrotoxicity is not an uncommon outcome in both short and long treatment courses. Intensive care unit need while on treatment, concurrent treatment with loop diuretic, underlying diagnosis with liver cirrhosis, and the initial trough level seem to be the main risk factors for nephrotoxicity. On the contrary, elevated baseline creatinine seemed to be protective. This observation could be due to the lack of mechanisms responsible for the development of nephrotoxicity in abnormal kidneys.
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Chapter 1

INTRODUCTION

Vancomycin is a glycopeptide antibiotic excreted by the kidney and is used to treat infections related to resistant gram positive organisms, mainly methicillin-resistant Staphylococcus aureus (MRSA), methicillin-resistant coagulase-negative staphylococci, and non-vancomycin resistant enterococci [1, 2]. Vancomycin was introduced to the clinical field in the 1950’s, but its use was limited due to its side effects, mainly nephrotoxicity, and the availability of alternative safer antibiotics.

Though vancomycin associated nephrotoxicity is a well-known clinical phenomenon, its mechanism is not well understood. Proximal renal tubular cell necrosis was suggested based on clinical observations and animal studies [3, 4, 5]. With the improved fermentation methods, vancomycin purity has increased from 70% to about 95%, thereby reducing drastically the severity of its toxicities, particularly nephrotoxicity [6-10].

Vancomycin use has dramatically increased over years due to changing resistant patterns along with the increasing number of infections. Currently vancomycin is a cornerstone antibiotic in the treatment of resistant gram positive bacteria related infections. Its wide use along with the recent changes in clinical practice toward higher dosing to achieve trough levels over 15 mg/ml raised concerns about its safety, especially the risk of nephrotoxicity [6, 7, 32].
To date vancomycin associated nephrotoxicity remains not fully understood with unclear data in regard to its true incidence and predisposing factors. Multiple studies have examined this issue but their results were limited by small sample size or the short treatment courses [2, 8, 9, 11-28].

In this study we are trying to overcome those limitations by studying a relatively larger population with longer treatment courses. The specific aims of this study are:

AIM 1) to estimate the incidence of vancomycin associated nephrotoxicity.

AIM 2) to identify risk factors associated with the development of vancomycin associated nephrotoxicity.
Chapter 2

METHODS

2.1 Study design and population

This is a retrospective study conducted among patients who were hospitalized and treated with vancomycin between 01/01/2007 and 07/31/2012 at Hershey Medical Center. As we are aiming to study the effects of long treatment courses we used the Infectious Diseases department’s OPAT (Outpatient antibiotic therapy) system to identify our patient population. During the study period, 783 unique patients received vancomycin at some point. We excluded patients below 18 years, those on hemodialysis, and those who had a documented creatinine value above or equal to 2 mg/dl either on admission or at the time when vancomycin was started. After applying those exclusion criteria we ended up with 681 unique patients. Of those, 102 had missing/insufficient creatinine data and were excluded. For those who received multiple courses of IV vancomycin only the first course was considered. After applying all above criteria we ended up with 579 unique treatment courses for 579 unique patients.

2.2 Data

Patients were identified through our OPAT system and relevant data were extracted from both OPAT system and medical records. Extracted data included (1) baseline characteristics of age in years, gender, height in centimeters, and weight in kilograms; (2) co-morbid conditions of hypertension, diabetes mellitus, coronary artery disease, liver cirrhosis, and stroke; (3) concurrent treatments that could be nephrotoxic or potentiate the
nephrotoxicity effect of vancomycin, those included concurrent treatment with loop diuretics (furosemide, and bumetanide), or aminoglycosides (amikacin, gentamicin, and tobramycin); (4) concurrent intravenous contrast administration; (5) underlying infection being treated, and those included the following categories listed according to their frequency: osteomyelitis, prosthetic joint infection, abscess, wound infection, intravascular device infection, endocarditis (both native valve and prosthetic), bacteremia, septic arthritis, cellulitis, meningitis, empyema or pneumonia. All creatinine values, vancomycin doses, times administered, start date, stop date, initial 24hrs dose in milligrams, initial trough level in mg/dl (level collected before the third, fourth, fifth or sixth dose), and highest trough level were collected.

Guided by definitions and classifications of acute kidney injury (AKI) of RIFLE and AKIN criteria [29, 30] and previous studies [2, 8, 9, 11, 16, 31], we defined vancomycin associated nephrotoxicity as an increase in the serum creatinine level by 0.5 mg/dL or 50% from baseline on at least two consecutive readings during vancomycin treatment course. Based on the creatinine values during the treatment course we identified those patients who met the definition for nephrotoxicity and documented the event date. Beside the occurrence of nephrotoxicity we also looked into time to toxicity defined as the time from starting vancomycin to the time nephrotoxicity definition was met.

Duration of treatment was considered from the time when first dose was given to the time that last dose was administered. For those who experienced nephrotoxicity, the date of event was regarded as the ending date of treatment. We identified vancomycin maintenance dose (milligrams per kilogram of body weight) defined as the last dosing
regimen/24 hrs before the end of the treatment course for those who did not develop nephrotoxicity. For those who developed nephrotoxicity their maintenance dose was the last dose/24hrs before they met the definition of nephrotoxicity. We also calculated baseline creatinine clearance based on Cockcroft-Gault equation, the ideal body weight (IBW) using Broca's formula, and the BMI (kg/m2).

Of note during the study period all treating physicians were aiming at dosing regimen to achieve treatment trough levels in compliance with the IDSA recommendations between 15-20 mg/dl for all the above mentioned diagnoses except for cellulites.

2.3 Statistical analysis plan

We summarized the data by descriptive statistics: mean/standard deviation for continuous variables, and frequency distribution for categorical variables. The incidence of nephrotoxicity was calculated for the overall study cohort. We also calculated the incidence in the first two weeks of treatment and the incidence after two weeks of treatment. To compare variables between the subjects who developed nephrotoxicity and those who did not, two-sample t-test was used for continuous variables, while chi-squared was used for proportions. Multiple logistic regression model was conducted to identify the variables that are independently associated with the development of nephrotoxicity. The magnitude of association was described by odds ratios and 95% confidence intervals. We used the SAS 9.1.3 to perform all analyses. The significance level of all statistical tests is set at 0.05 level.
3.1 Study population

Our population of 579 patients has a median age of 55.3 years (median of 56 years, and inter quartile range {IQR}, 44-68 years). The baseline creatinine mean is 0.88mg/dl (median 0.83mg/dl, and inter quartile range {IQR}, 0.65-1.02 mg/dl). Around 73% of our study population received an initial (24hrs) vancomycin dose of 2000mg (mean is 2042mg standard deviation is 483mg). Initial trough was available for 482 patients which constitute around 83% of the total population. Weight was documented for 568 (98%) patients of our study population, and height for 504 (87%). The mean duration of therapy is 30 days (median is 26 days, and inter quartile range {IQR}, 7-43 days). Males constituted 337 (58.2%) of our population. 274 (47.3%) of the whole population carried a diagnosis of hypertension, 163 (28.2%) were diabetic, 133 (23%) with ischemic heart disease, 85 (14.7%) with heart failure, and 2.9% had a history of stroke. During the treatment course, 140 (24.2%) of study population spent some time in the intensive care unit, 175 (30.2%) received IV contrast at least once, 104 (18%) were on loop diuretics, and only 22 (3.8%) were concurrently treated with aminoglycoside. (See table 1)

<table>
<thead>
<tr>
<th></th>
<th>Study population</th>
<th>No Nephrotoxicity</th>
<th>Nephrotoxicity</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>55.3 (17.0)</td>
<td>55.2 (16.9)</td>
<td>55.6 (17.0)</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>Sex (Female)</strong></td>
<td>242 (41.8%)</td>
<td>167 (39.3%)</td>
<td>75 (48.7%)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Column 1</td>
<td>Column 2</td>
<td>Column 3</td>
<td>Column 4</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>89.9 (25.9)</td>
<td>89.9 (25.7)</td>
<td>89.7 (26.6)</td>
<td>0.95</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170.8 (11.6)</td>
<td>171.7 (11.3)</td>
<td>168.3 (12.2)</td>
<td>0.0036</td>
</tr>
<tr>
<td>Body mass index BMI (Kg/m²)</td>
<td>31.0 (8.4)</td>
<td>30.7 (8.2)</td>
<td>31.8 (9.0)</td>
<td>0.2026</td>
</tr>
<tr>
<td>Ideal body weight IBW (Kg)</td>
<td>70.0 (8.7)</td>
<td>70.7 (8.4)</td>
<td>68.4 (9.3)</td>
<td>0.0096</td>
</tr>
<tr>
<td>Baseline creatinine (mg/dl)</td>
<td>0.88 (0.31)</td>
<td>0.90 (0.31)</td>
<td>0.83 (0.31)</td>
<td>0.016</td>
</tr>
<tr>
<td>Baseline creatinine Clearance</td>
<td>100.4 (45.0)</td>
<td>98.8 (44.1)</td>
<td>104.9 (47.2)</td>
<td>0.1786</td>
</tr>
<tr>
<td>Initial dose (mg/kg IBW)</td>
<td>29.8 (8.2)</td>
<td>29.3 (7.5)</td>
<td>31.2 (9.8)</td>
<td>0.042</td>
</tr>
<tr>
<td>Initial dose (mg/kg Wt)</td>
<td>24.5 (8.7)</td>
<td>24.3 (8.6)</td>
<td>25.0 (9.0)</td>
<td>0.42</td>
</tr>
<tr>
<td>Initial trough (mg/dl)</td>
<td>11.4 (6.0)</td>
<td>11.0 (5.7)</td>
<td>12.4 (6.6)</td>
<td>0.0463</td>
</tr>
<tr>
<td>Highest trough (mg/dl)</td>
<td>20.9 (8.8)</td>
<td>19.4 (8.1)</td>
<td>24.9 (9.3)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Maintenance dose (mg/kg IBW)</td>
<td>31.0 (13.0)</td>
<td>30.6 (11.6)</td>
<td>32.2 (16.3)</td>
<td>0.3024</td>
</tr>
<tr>
<td>Maintenance dose (mg/kg Wt)</td>
<td>25.5 (12.4)</td>
<td>25.3 (11.6)</td>
<td>26.2 (14.3)</td>
<td>0.5</td>
</tr>
<tr>
<td>Duration of therapy (days)</td>
<td>23.9 (23.4)</td>
<td>26.9 (24.6)</td>
<td>15.6 (17.3)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>ICU</td>
<td>140 (24.2%)</td>
<td>79 (18.6%)</td>
<td>61 (39.6%)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

**Co-morbid condition**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Column 1</th>
<th>Column 2</th>
<th>Column 3</th>
<th>Column 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>274 (47.3%)</td>
<td>194 (45.6%)</td>
<td>80 (52%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>163 (28.2%)</td>
<td>119 (28.0%)</td>
<td>44 (28.6%)</td>
<td>0.89</td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td>133 (23.0%)</td>
<td>91 (21.4%)</td>
<td>42 (27.3%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>85 (14.7%)</td>
<td>54 (12.7%)</td>
<td>31 (20.1%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Stroke</td>
<td>17 (2.9%)</td>
<td>10 (2.4%)</td>
<td>7 (4.6%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Chronic Liver Disease</td>
<td>20 (3.5%)</td>
<td>11 (2.6%)</td>
<td>9 (5.8%)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

**Treatment indication**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Column 1</th>
<th>Column 2</th>
<th>Column 3</th>
<th>Column 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteomyelitis</td>
<td>170 (29.4%)</td>
<td>125 (29.4%)</td>
<td>45 (29.2%)</td>
<td>1</td>
</tr>
<tr>
<td>Prosthetic joint infection</td>
<td>102 (17.6%)</td>
<td>78 (18.4%)</td>
<td>24 (15.6%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Abscess</td>
<td>81 (14.0%)</td>
<td>54 (12.7%)</td>
<td>27 (17.5%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Wound infection</td>
<td>56 (9.7%)</td>
<td>47 (11.1%)</td>
<td>9 (5.8%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Intravascular device infection</td>
<td>39 (6.7%)</td>
<td>30 (7.1%)</td>
<td>9 (5.8%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>34 (5.9%)</td>
<td>21 (4.9%)</td>
<td>13 (8.4%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>32 (5.2%)</td>
<td>22 (5.2%)</td>
<td>10 (6.5%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Condition</td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 3</td>
<td>p-value</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>23 (4.0%)</td>
<td>19 (4.5%)</td>
<td>4 (2.6%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>18 (3.1%)</td>
<td>14 (3.3%)</td>
<td>4 (2.6%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Meningitis</td>
<td>11 (1.9%)</td>
<td>7 (1.7%)</td>
<td>4 (2.6%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Pneumonia/Empyema</td>
<td>13 (2.25%)</td>
<td>8 (1.9%)</td>
<td>5 (3.3%)</td>
<td>0.35</td>
</tr>
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</table>

Co-administered treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic</td>
<td>104 (18%)</td>
<td>62 (14.6%)</td>
<td>42 (27.3%)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>22 (3.8%)</td>
<td>13 (3.1%)</td>
<td>9 (5.8%)</td>
<td>0.12</td>
</tr>
<tr>
<td>IV contrast use</td>
<td>175 (30.2%)</td>
<td>118 (27.8%)</td>
<td>57 (37.0%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

3.2 Incidence of nephrotoxicity

In our total study population 154 patients (26.6%) met the diagnosis of vancomycin associated nephrotoxicity; of those, 90 (15.5%) met the diagnosis in the initial 14 days of vancomycin treatment and the rest 64 (11.1%) met the definition after 14 days of treatment. The median time for nephrotoxicity was 9 days (IQR 4-21 days).

3.3 Factors associated with nephrotoxicity

To a large extent providers at our institution used an initial vancomycin dose of 1000 mg every 12hrs and then adjusted the dose based on the initial trough level; so as expected there was no statistical difference between the patients who experienced nephrotoxicity compared to the rest of the population in regard to the mean initial vancomycin dose.

No statically significant difference was observed in terms of patient's mean weight, and so for initial dose per weight over the first 24hrs of treatment (25mg/kg vs. 24.3 mg/kg; P= 0.42). We observed a statistically significant difference between those who experienced a nephrotoxic event compared to those who did not in terms of the mean height (168cm vs. 170cm).
172cm). This was reflected in a lower ideal body weight among those who developed nephrotoxicity (68.4kg vs. 70.7kg; P = 0.01); in other words those who had a nephrotoxic event were exposed to a higher vancomycin dose per ideal body weight (31.2mg/kg vs. 29.3; P = 0.04). Those who experienced nephrotoxicity had a higher initial trough level (12.4mg/dl vs. 11.0; P = 0.046). (See table 1)

Interestingly and unexpectedly patients who experienced nephrotoxic events had a statistically significant lower baseline creatinine value (0.83mg/dl vs. 0.90mg/dl; P = 0.016). The interpretation of the significant difference between the group which experienced nephrotoxic event and the rest of the population in regards to highest trough level (24.9mg/dl vs. 19.4mg/dl P < 0.0001) is challenging, as the high trough levels could have potentially caused the event or it could have been secondary to it. The significant "shorter duration" for those who developed the nephrotoxic event compared to those who did not (15.6 days vs. 26.9 days; P < 0.0001) is likely to be related to the timing of the event.

There was no statistical difference between those who developed nephrotoxicity and the rest of the study population in regards to the patient’s mean age (55.6 years vs. 55.2; P = 0.83), body mass index BMI (31.8 vs.30.7; P = 0.2), or maintenance vancomycin dosing (26.2 mg/kg vs. 25.3 mg/kg; P = 0.5).

In our study population we found a statistically strong association between admission to the intensive care unit and the occurrence of vancomycin associated nephrotoxicity (OR, 2.13; 95% confidence interval, 1.6-2.8; P < 0.0001). Females experienced a higher rate of nephrotoxic events compared to males (OR, 1.24; 95% confidence interval, 1.01-1.5; P = 0.04). A statically significant association was also found between vancomycin associated
nephrotoxicity and carrying a diagnosis of heart failure (OR, 1.58; 95% confidence interval, 1.06-2.37; P = 0.026), concurrent loop diuretic use (OR, 1.87; 95% confidence interval, 1.32-2.64; P = 0.0004), and intravenous contrast dye use (OR, 1.33; 95% confidence interval, 1.03-1.72; P = 0.032). More of those who carried a diagnosis of liver cirrhosis developed nephrotoxicity compared to those who did not (5.8% vs. 2.6%), though the association did not reach statistical significance of 0.05 (OR, 2.26; 95% confidence interval, 0.95-5.35; P = 0.058). (See table 1)

Other associations that did not reach statistical significance were hypertension (OR, 1.14; 95% confidence interval, 0.95-1.37; P = 0.18), ischemic heart disease (OR, 1.3; 95% confidence interval, 0.93-1.75; P = 0.14), diabetes (OR, 1.02; 95% confidence interval, 0.76-1.37; P = 0.89), stroke (OR, 1.9; 95% confidence interval, 0.75-4.99; P = 0.17), and concurrent use of aminoglycosides (OR, 1.9; 95% confidence interval, 0.83-4.38; P = 0.12). In regard to the indication for therapy, none of the underlying infections had a significant statistical association with the development of nephrotoxicity. (See table 1)

3.4 Independent predictors of nephrotoxicity

We conducted multiple logistic regression analysis using a stepwise selection method. All clinically significant variables with P values < 0.3 from bivariate analyses were entered in the model. Admissions to the intensive care unit, baseline creatinine, concurrent use of loop diuretics, and co-morbid conditions of liver cirrhosis were independently associated with the development of nephrotoxicity. This was also the case with initial trough level though the adjusted P value was slightly above the significance level of 0.05 (P value = 0.08). (See table 2)
Table 2: Estimation results of multivariable logistic regression model

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>95% Confidence limits</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU need</td>
<td>2.77</td>
<td>1.67 - 4.60</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Baseline creatinine</td>
<td>0.24</td>
<td>0.10 - 0.58</td>
<td>0.0016</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>2.43</td>
<td>1.39 - 4.28</td>
<td>0.002</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>3.58</td>
<td>1.25 - 10.20</td>
<td>0.017</td>
</tr>
<tr>
<td>Initial trough</td>
<td>1.04</td>
<td>1.00 - 1.09</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Among those factors the association between baseline creatinine and nephrotoxicity was the most interesting. We found that higher baseline creatinine was protective against nephrotoxicity (OR, 0.24; 95% confidence interval, 0.1-0.58; P = 0.0016). When we repeated the logistic regression analysis after choosing a creatinine value of 0.8mg/dl as a cutoff point to group the study population into low baseline creatinine (less than or equal to 0.8mg/dl) and high baseline creatinine (more than 0.8mg/dl), we got similar results (OR, 0.40; 95% confidence interval, 0.25-0.66; P = 0.0003).
Vancomycin associated nephrotoxicity is not an uncommon outcome in both short and long treatment courses. Previous studies have observed different incidence rates that highly varied from < 10% in some studies to > 30% in others with an incidence that correlated with vancomycin dosing and trough level [9, 14, 16, 19, 25, 33]. In our study population 26.6% developed nephrotoxicity while being treated with vancomycin. Of those, 58.3% (15.5% of the total population) developed nephrotoxicity within the first two weeks of treatment.

Intensive care unit need while on treatment, concurrent treatment with loop diuretic, underlying diagnosis with liver cirrhosis, and the initial trough level seem to be the main risk factors for nephrotoxicity. On the contrary, having abnormal kidney function test (elevated baseline creatinine) to start with seemed to be protective even after adjusting for the confounding effects of age, sex, weight, height, initial dose/weight, maintenance dose/weight, initial trough, co morbid chronic illnesses, concurrent aminoglycoside, and loop diuretic use as well as the need to be in the intensive care unit. Patients with baseline creatinine equal to or below 0.8mg/dl seem to have 2.5 times the risk of developing nephrotoxicity compared to those with a baseline creatinine above 0.8mg/dl.

Vancomycin is renally eliminated mainly via glomerular filtration, and to some extent via active tubular secretion [34]. The latter is proposed to play the major role in nephrotoxicity [35]. Animal studies suggested oxidative stress might underlie the pathogenesis of
vancomycin-induced toxicity [4, 36, 37]. It could be that patients with higher baseline creatinine lack the mechanisms responsible for the development of nephrotoxicity.

What are unique about our study are the good sample size and the large proportion of long treatment courses. We had to exclude one hundred and two individuals at the beginning of the study due to the lack of baseline creatinine, or creatinine values at the end of the treatment course. It seems that the providers had a low suspicion for nephrotoxicity in those individuals and were not compelled to check for nephrotoxicity. This might have led to overestimation in our incidence rate. For the 579 patients who were included, missing data were limited due to the excellent and extensive recording of the study variables. A large proportion of our population was treated for chronic orthopedic infections. This might limit the generalizability of our results. A large prospective multi-center trial will potentially overcome our limitations. Animal studies to evaluate the effect of baseline creatinine on the risk of vancomycin associated nephrotoxicity will be of great help.
References

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