Comparison of the Difference in Nephrotoxicity between Nafcillin and Piperacillin-Tazobactam

Sonali Kishor Patel

University of Kentucky
STUDENT AGREEMENT:

I represent that my thesis or dissertation and abstract are my original work. Proper attribution has been given to all outside sources. I understand that I am solely responsible for obtaining any needed copyright permissions. I have obtained and attached hereto needed written permission statements(s) from the owner(s) of each third-party copyrighted matter to be included in my work, allowing electronic distribution (if such use is not permitted by the fair use doctrine).

I hereby grant to The University of Kentucky and its agents the non-exclusive license to archive and make accessible my work in whole or in part in all forms of media, now or hereafter known. I agree that the document mentioned above may be made available immediately for worldwide access unless a preapproved embargo applies.

I retain all other ownership rights to the copyright of my work. I also retain the right to use in future works (such as articles or books) all or part of my work. I understand that I am free to register the copyright to my work.

REVIEW, APPROVAL AND ACCEPTANCE

The document mentioned above has been reviewed and accepted by the student's advisor, on behalf of the advisory committee, and by the Director of Graduate Studies (DGS), on behalf of the program; we verify that this is the final, approved version of the student's dissertation including all changes required by the advisory committee. The undersigned agree to abide by the statements above.

Sonali Kishor Patel, Student
Daniela Moga, MD, PhD, Major Professor
Corrine Williams, ScD, MS, Director of Graduate Studies
Comparison of the Difference in Nephrotoxicity between Nafcillin and Piperacillin-Tazobactam

CAPSTONE PROJECT PAPER

A paper submitted in partial fulfillment of the requirements for the degree of Master of Public Health in the University of Kentucky College of Public Health By Sonali Kishor Patel 860 Wolf Hills Boulevard Henderson, Kentucky

Lexington, Kentucky April 19, 2016

Daniela Moga, MD, PhD, Chair Craig Martin, PharmD, MBA, BCPS-AQID Lorie Chesnut, DrPH, MPH David Mannino, MD

Abstract word count: 356
Text word count: 3,026
Table of Contents

Abstract.......................................................................................................................... 3
Introduction................................................................................................................... 5
Methods.......................................................................................................................... 7
Results........................................................................................................................... 11
Discussion................................................................................................................... 14
Conclusion................................................................................................................... 18
References................................................................................................................... 19
Tables and Figures........................................................................................................ 24
Acknowledgements...................................................................................................... 30
Biographical Sketch...................................................................................................... 31
Abstract

Objective
To evaluate whether nephrotoxicity differs between nafcillin and piperacillin-tazobactam in adult hospitalized patients.

Introduction
Acute kidney injury (AKI) is a significant cause of morbidity and mortality in the inpatient setting, with antibiotics being a significant contributor. There is evidence of an increased risk of nephrotoxicity with the combination of vancomycin and piperacillin-tazobactam compared to vancomycin and cefepime or vancomycin alone. It is unknown whether this effect is exclusive for piperacillin-tazobactam. Therefore, in order to promote optimal medication therapy for inpatient bacterial infections, there is a need to assess the persistence of this difference in other beta-lactam antibiotics.

Methods
A single-center, retrospective cohort study was performed utilizing electronic health records at University of Kentucky Healthcare. Adult hospitalized patients being treated with nafcillin or piperacillin-tazobactam from September 1, 2010 to September 1, 2014 were included in the study. Age, sex, Charlson Comorbidity Index, baseline creatinine clearance, dehydration, hypotension, exposure to concomitant nephrotoxins, and duration of therapy were evaluated. The primary outcome was AKI as defined by the RIFLE criteria (risk, injury, failure, loss of kidney function, and end-stage kidney disease), where risk, injury, and failure were defined as a 25%,
50%, and 75% decrease in glomerular filtration rate from baseline, respectively. Secondary outcomes included time to AKI from initiation of antibiotics, hospital length of stay, and mortality.

Results

Of the 3,393 patients included in this study, 272 were treated with nafcillin and 3,121 were treated with piperacillin-tazobactam. Overall incidence of AKI was 19.49% in the nafcillin group and 7.72% in the piperacillin-tazobactam group (p<0.0001). After adjusting for age, sex, Charlson Comorbidity Index, baseline creatinine clearance, hypotension, number of concomitant nephrotoxins, and duration of therapy, those in the nafcillin group had 2.002 (95% CI 1.357-2.953) times the odds of AKI compared to those in the piperacillin-tazobactam group. Time to AKI, hospital length of stay, and inpatient mortality were also significantly higher in the nafcillin group.

Conclusions

The results from this study suggest that nafcillin has a significantly greater potential for nephrotoxicity compared to piperacillin-tazobactam. Future research may involve further evaluating the risk factors of AKI, indication, and dosing schedule of these or other antibiotics in a larger population.
Introduction

The incidence of acute kidney injury (AKI) is estimated to be between 5.7% and 18.0%. Development of AKI can lead to significant increases in length of stay, healthcare costs, and mortality, with in-hospital mortality ranging from 50.5% to 76.8%. AKI can occur as a result of a number of factors including cardiac insufficiency, sepsis, malignancy, liver insufficiency, and autoimmune diseases. Drug-induced nephrotoxicity is also a significant cause of AKI and has been shown to be associated with angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), acyclovir, aminoglycosides, amphotericin B, beta-lactam antibiotics, IV contrast, and non-steroidal anti-inflammatory drugs (NSAIDs), among others. Piperacillin-tazobactam is a beta-lactam/beta-lactamase inhibitor combination broad-spectrum antibiotic commonly used to empirically treat for many gram-positive and gram-negative infections. Incidence of nephrotoxicity in piperacillin-tazobactam has been reported to be 9.0% to 18.2%. There is little data demonstrating the mechanism of nephrotoxicity of piperacillin-tazobactam, although in few studies indicate acute interstitial nephritis (AIN) is the most likely cause. Piperacillin-tazobactam has also been shown to cause a lower rate of renal recovery compared to other antibiotics. The combination of vancomycin, a glycopeptide antibiotic used to treat gram-positive infections, with piperacillin-tazobactam has a higher incidence of nephrotoxicity than vancomycin alone. In yet to be published data from a study conducted at the University of Kentucky, the combination of vancomycin and piperacillin-tazobactam also had a higher incidence of
nephrotoxicity than combination of vancomycin and cefepime, another broad-spectrum beta-lactam antibiotic. It is unknown whether this effect is exclusive for piperacillin-tazobactam or if it also exists in other beta-lactam antibiotics.

Nafcillin is a narrow-spectrum beta-lactam antibiotic used most commonly as one of the first line treatments for methicillin-sensitive *Staphylococcus aureus* (MSSA) infections. Incidence of nephrotoxicity of nafcillin has been shown to be 11.4%. Nafcillin has been reported as the most probable cause of acute interstitial nephritis (AIN) in a number of cases.

The purpose of this study is to investigate the difference in nephrotoxicity between nafcillin and piperacillin-tazobactam in adult hospitalized patients. The results of this study may aid in the selection of medication therapy for inpatient bacterial infections.
Methods

Study sample

A single-center, retrospective cohort study was conducted at University of Kentucky Healthcare, a tertiary care academic medical center. All patients admitted between September 1, 2010 and September 1, 2014 without renal dysfunction at initiation, chronic kidney disease, structural kidney disease, or pre-existing dialysis were eligible for the study. Patients with kidney disease at baseline were excluded to allow for assessment of the effects of the study antibiotics. Each admission was treated as an independent event. Patients receiving either nafcillin or piperacillin-tazobactam were included. Patients were excluded from the piperacillin-tazobactam group if they received therapy with vancomycin in order to isolate the effects of the study drug. Those in the nafcillin group may have received up to 5 days of vancomycin or piperacillin-tazobactam to remain in the study due to clinical use of nafcillin typically being after initial treatment with more broad-spectrum empiric therapy. Other exclusion criteria include length of stay less than 2 days, age less than 18 years, baseline creatinine clearance greater than 4 times the standard deviation of the mean or less than 30 mL/min, days of antibiotic therapy less than 2 days, and AKI prior to treatment index, within 48 hours of treatment index, or greater than 7 days after treatment was discontinued. Minimum limits were used for length of stay and duration of antibiotic therapy to exclude AKI events due to previous exposures. These criteria were applied for timeframe of AKI to limit events to those that occurred due to the study drugs. Patients who did not have serum creatinine values were also excluded from analysis. This study was exempt from IRB approval as only de-identified data were used.
Data collection and measures

Inpatient clinical data from September 1, 2010 to September 1, 2014 was gathered from the University of Kentucky Center for Clinical and Translational Science Enterprise Data Trust. Information on age, sex, Charlson Comorbidity Index, baseline creatinine clearance, dehydration, hypotension, receipt of concomitant nephrotoxins, and duration of antibiotic therapy were collected. Many of these factors have the potential to increase risk of AKI. Charlson Comorbidity Index is a measure of illness severity based on a patient’s medical history. Baseline creatinine clearance was based on the first measured serum creatinine. Hypotension was determined by the composite of hypotension diagnosis, mean arterial pressure less than 60 mmHg, and/or use of vasopressor or inotrope therapy. Concomitant nephrotoxins assessed include acyclovir, aminoglycosides, amphotericin B, ACEIs, ARBs, colistin, cyclosporine, foscarnet, IV contrast, loop diuretics, NSAIDS, sulfonamides, tacrolimus, and tenofovir. Patients received one point for each of the nephrotoxins studied to give a total number of concomitant nephrotoxins received. Duration of therapy was defined as the number of unique days patient received at least one dose of study antibiotic.

Study outcomes

The primary outcome was the difference in AKI between nafcillin and piperacillin-tazobactam as defined by the RIFLE criteria based on percent change from baseline creatinine clearance to minimum creatinine clearance. This was evaluated both in patients being treated with nafcillin with exposure to piperacillin-tazobactam and/or vancomycin for 5 days or less, as well as the
nafcillin only group. The RIFLE criteria is the first consensus definition of AKI. Within the RIFLE criteria there are 3 severity classes, risk, injury, and failure, which are a 25%, 50%, and 75% decrease in glomerular filtration rate (GFR) from baseline. GFR is a measure of kidney function and is based on the adjusted Cockcroft-Gault equation. In addition, there are two outcome classes, loss of kidney function and end-stage kidney disease. The current study did not evaluate outcome classes because diagnosis based on duration of renal dysfunction is required, a variable that was not collected. The RIFLE criteria has been largely validated to identify AKI, classify severity, and correlate with patient outcome.

Secondary outcomes include time to AKI from initiation of antibiotic therapy, hospital length of stay, and mortality, where mortality is a composite of inpatient mortality and transfer to hospice service.

Statistical analysis

Basic descriptive statistics were used to assess the characteristics of the study population. Continuous variables were evaluated by Student’s T-test or, if data was not normally distributed, Wilcoxon Rank Sum test. Data from continuous variables were reported as mean and standard deviation as well as median with interquartile range. Categorical variables were analyzed using Chi-Square test or, if there was a count of less than 5 in one of the cells of the contingency table or if 25% or more cells had expected counts less than 5, results from Fisher's Exact test were reported. Data from categorical variables were reported as number and percentage. All tests were two-sided with significance defined as $p < 0.05$. Chi-Square test and Fisher’s Exact test were
also used for the unadjusted analysis of the primary outcome of AKI overall and for risk, injury, and failure classifications. Logistic regression was used for an adjusted analysis of the primary outcome of AKI overall and for risk, injury, and failure classifications. Adjustment was made for all variables that reached statistical significance in the bivariate analysis. Secondary outcomes were analyzed using Student’s T-test or Wilcoxon Rank Sum test for continuous variables and Chi-Square test for categorical variables. All statistical analysis was performed using SAS Statistical software.
Results

A total of 31,854 patients were screened for study participation (Figure 1). Based on antibiotic exposure, length of stay less than 2 days, age less than 18 years, lack of serum creatinine values, baseline creatinine clearance greater than 4 times the standard deviation of the mean (~406 mL/min) or less than 30 mL/min, days of therapy less than 2 days, and AKI prior to treatment index, within 48 hours of treatment index, or greater than 7 days after treatment was discontinued, 28,461 patients were excluded. The final sample consisted of 272 patients in the nafcillin study group and 3,121 patients in the piperacillin-tazobactam study group.

Patient population

The mean age of patients in the nafcillin group was 47.49 ± 15.61 years and 53.28 ± 17.56 years in the piperacillin-tazobactam group (p<0.0001) (Table 1). There were 64.34% males in the nafcillin group and 49.15% in the piperacillin-tazobactam group (<0.0001). Charlson Comorbidity Index was also statistically different between groups, with a mean score of 2.77 ± 3.19 in the nafcillin group and 3.47 ± 3.65 in the piperacillin-tazobactam group (p=0.0084). Mean baseline creatinine clearance was 106.91 ± 42.73 mL/min in the nafcillin group and 100.38 ± 42.87 in the piperacillin-tazobactam group (p=0.0161). Hypotension was observed in 51 (18.75%) of patients in the nafcillin group and 342 (10.96%) in the piperacillin-tazobactam group (p=0.0001). Exposure to concomitant nephrotoxins was significantly different for ACEIs, acyclovir, aminoglycosides, loop diuretics, NSAIDS, sulfonamides, tacrolimus, IV contrast, with all but tacrolimus being higher in nafcillin. There was no colistin use in either group. The
number of patients receiving 2, 3, and 4 or more concomitant nephrotoxins was also greater in
the nafcillin group (p<0.0001). Mean duration of therapy was longer in the nafcillin group, 8.46
± 9.96 days, compared to in the piperacillin-tazobactam group, 4.63 ± 2.67 days (p<0.0001). The
number of patients transferred to University of Kentucky Healthcare from an outside hospital
was 1,306 (38.49%), with a similar proportion in each group. There were no patients that
developed need for dialysis while inpatient.

Table 2 displays the antibiotic exposure for both study groups. In the nafcillin group, there were
two patients (0.74%) who received piperacillin-tazobactam, 90 (33.09%) who received
vancomycin, and 139 (51.10%) who received both piperacillin-tazobactam and vancomycin. 41
(15.07%) patients received nafcillin only.

*Primary outcome*

In the unadjusted analysis, AKI occurred in 53 (19.49%) nafcillin patients and 241 (7.72%)
piperacillin-tazobactam patients (p<0.0001). There were 38 (13.97%) patients classified as
having risk in the nafcillin group and 192 (6.15%) in the piperacillin-tazobactam group. Ten
(3.68%) of patients were classified as having injury in the nafcillin group and 37 (1.19%) in the
piperacillin-tazobactam group. Finally, 5 (1.84%) were classified as having failure in the
nafcillin group and 12 (0.38%) in the piperacillin-tazobactam group. All categories had higher
incidence of nephrotoxicity in the nafcillin group. In the nafcillin only group, AKI occurred in 9
patients (21.95%) compared to 241 (7.72%) in the piperacillin-tazobactam group (p<0.0001)
(Table 3).
Adjustments were made for age, sex, Charlson Comorbidity Index, baseline creatinine clearance, hypotension, number of concomitant nephrotoxins, and duration of therapy. In the adjusted analysis, those in the nafcillin group had 2.002 (95% CI 1.357-2.953) times the odds of AKI compared to those in the piperacillin-tazobactam group. Results were similar in the risk category with the nafcillin group having 1.799 (95% CI 1.162-2.786) times the odds of risk compared to those in the piperacillin-tazobactam group. The injury and failure categories were non-significant with odds ratios of 2.246 (95% CI 0.958-5.264) and 2.357 (95% CI 0.685-8.113), respectively. The odds of AKI in the nafcillin only group was 2.634 (95% CI 1.154-6.016) times that of the piperacillin-tazobactam group (Table 4).

*Secondary outcomes*

The mean time to AKI was 6.00 ± 5.14 days in the nafcillin group and 4.69 ± 3.41 days in the piperacillin-tazobactam group (p=0.0458). The mean hospital length of stay was 14.38 ± 12.69 days in the nafcillin group and 7.44 ± 7.55 days in the piperacillin-tazobactam group (p<0.0001). Mortality occurred in 135 (3.98%) patients in the total study population, with 23 (8.46%) in the nafcillin group and 112 (3.59%) in the piperacillin-tazobactam group (p<0.0001) (Table 5).
Discussion

This study aimed to evaluate whether nephrotoxicity differs between nafcillin and piperacillin-tazobactam. The nafcillin group had 2.002 (95% CI 1.357-2.953) times the odds of AKI compared to the piperacillin-tazobactam group after adjusting for age, sex, Charlson Comorbidity Index, baseline creatinine clearance, hypotension, number of concomitant nephrotoxins, and duration of therapy. This difference persisted in the risk category, however was not statistically significant in the injury and failure categories. A similar result was seen when limiting comparison to those who received nafcillin only. This study suggests that beta-lactam antibiotics overall may contribute to nephrotoxicity in adult hospitalized patients, with nafcillin carrying a significantly larger burden of AKI than piperacillin-tazobactam.

Results from this study agree with current literature, although the incidence of AKI in nafcillin was higher compared to previous studies. In a yet to be published study from the University of Kentucky, vancomycin in combination with piperacillin-tazobactam had a significantly higher incidence of nephrotoxicity than vancomycin in combination with cefepime, with rates of 30% and 18%, respectively (p<0.0001). The incidence of AKI was also shown to be different depending on the dosing scheme of piperacillin-tazobactam, with a higher rate in those who received 4.5 grams every 6 hours compared to those who received 3.375 grams every 6 hours. In a study evaluating a population of diabetic patients with osteomyelitis, acute renal failure was seen in 29.3% of patients being treated with combination of vancomycin with piperacillin-tazobactam compared to 13.3% in patients treated with vancomycin in combination with cefepime. In a third study, incidence of AKI was 34.8% in the vancomycin and piperacillin-
tazobactam combination group compared to 12.5% in the vancomycin and cefepime group.\textsuperscript{30} There is also evidence of an increase in incidence of nephrotoxicity of vancomycin in combination with piperacillin-tazobactam compared to vancomycin alone.\textsuperscript{6,15,25,26}

There are a number of limitations associated with this study. This was a single center study conducted at University of Kentucky Healthcare and, therefore, results may not be generalizable to other hospitals serving different populations with differing levels of acuity. In addition, due to the retrospective nature of this study, there are many variables with potential to affect results that were unable to be collected, leading to residual confounding. One of these includes indication for antibiotics or microbiology results. Piperacillin-tazobactam is a broad-spectrum antibiotic that is often used for empiric therapy when an infection is suspected, however culture and susceptibilities or source of infection are unknown. Once more information is known about an infection, therapy is often switched to a more narrow-spectrum antibiotic such as nafcillin for an MSSA infection. This is likely the reason the number of patients in each group is different with the sample size in nafcillin being significantly smaller. This may also lead to nafcillin being used for longer durations compared to piperacillin-tazobactam, which may only be used for a short period of time before switching to an antibiotic targeting a specific bacterium.

Another limitation is temporality. This study assessed exposure to concomitant nephrotoxins, hypotension, and dehydration at any point during a patient’s hospital stay rather than in relation to development of AKI. The amount and duration of exposure was not analyzed, and exposure to different nephrotoxins was treated the same and combined into a number of concomitant nephrotoxins group, although different medications may have differing levels of nephrotoxicity.
This study excluded patients in the piperacillin-tazobactam group who received vancomycin, however included patients in the nafcillin group if they received up to 5 days of therapy with vancomycin or piperacillin-tazobactam. This was due to the clinical use of nafcillin typically being after initial treatment with a more broad-spectrum antibiotic such as piperacillin-tazobactam and/or vancomycin. The differing levels of exposure to vancomycin is another limitation of this study and may have an effect on the odds of nephrotoxicity in nafcillin. Exposure to vancomycin was excluded in the piperacillin-tazobactam group to try to isolate the effect of the study drug. However, nephrotoxicity due to vancomycin is not expected to develop within that timeframe; it has been shown that nephrotoxicity occurs after 7 days of therapy.\(^\text{27}\) Interestingly, time to AKI was longer in nafcillin, which is not what would be expected if exposure to vancomycin was contributing to this effect.

Additionally, for patients transferred in from an outside hospital, information about their previous hospital stay prior to coming to University of Kentucky Healthcare was not available to be evaluated.

Another possible limitation is use of the RIFLE criteria as a measure of nephrotoxicity. Prior to the introduction of the RIFLE criteria in 2004, a number of definitions of AKI were used. The RIFLE criteria has been largely validated to identify AKI, classify severity, and correlate with patient outcome.\(^\text{21-24}\) There has been an almost linear relationship seen between risk classification in the RIFLE criteria and hospital mortality.\(^\text{23}\) The RIFLE criteria is limited by its requirement of baseline renal function, or an estimate from the Modification of Diet in Renal Disease (MDRD) equation. It has been modified in an attempt to increase sensitivity and specificity with the Acute
Kidney Injury Network (AKIN) criteria, which was introduced in 2007. With the AKIN criteria, baseline serum creatinine is not required. However, AKIN criteria could not be used in this study because it requires adequate hydration status in order to diagnose AKI, which could not be ensured due to the retrospective nature of this study.\textsuperscript{28} Although these limitations exist, it has been shown that these two classification schemes are largely similar in identifying AKI and have no difference in ability to predict mortality.\textsuperscript{29-31} Creatinine clearance is used to estimate GFR, however it itself has limitations in its ability to measure kidney function. Biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) are currently being investigated as new ways to classify AKI earlier.\textsuperscript{32-34}
**Conclusion**

The odds of AKI overall and risk classification were higher in the nafcillin group compared to the piperacillin-tazobactam group, although this difference did not persist in the injury and failure categories. The mean time to AKI and hospital length of stay were longer in nafcillin patients, and the incidence of mortality was also higher in the nafcillin group. This study suggests that beta-lactam antibiotics overall may contribute to nephrotoxicity in adult hospitalized patients, with nafcillin carrying a significantly greater potential for AKI than piperacillin-tazobactam. However, further analysis should be done to assess the impact of risk factors in contributing to this rate of nephrotoxicity since patients in the nafcillin group had greater exposure to concomitant nephrotoxins and a longer duration of therapy. Future research should further evaluate the findings of this study with a larger population assessing important variables that could not be analyzed, such as site and type of infection and time and duration of exposure to concomitant nephrotoxins, hypotension, and dehydration in relation to development of AKI. It may also be beneficial to compare other beta-lactams or different dosing schemes.
References


16. Youngster I, Shenoy ES, Hooper DC, Nelson SB. Comparative evaluation of the tolerability of cefazolin and nafcillin for treatment of methicillin-susceptible


Tables and Figures

Figure 1: Sample Selection

31,854 total patients screened

28,461 patients excluded:
- 3,410 length of stay < 2 days
- 42 patient age < 18 years
- 15,211 patients did not receive nafcillin or piperacillin-tazobactam
- 8,655 patients received piperacillin-tazobactam with vancomycin
- 168 nafcillin patients with adjunct treatment > 5 days
- 40 patients with no serum creatinine values
- 7 patients with baseline CrCl > 4 SD + mean (~406 mL/min)
- 148 patients with baseline CrCl < 30 mL/min
- 553 patients with antibiotic days of therapy < 2 days
- 64 patients had an AKI prior to treatment index
- 150 patients had an AKI within 48 hours of treatment index
- 13 patients had an AKI > 5 days after treatment discontinued

3,121 patients in piperacillin-tazobactam study group

272 patients in nafcillin study group
Table 1: Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall n=3393</th>
<th>Nafcillin group n=272</th>
<th>Piperacillin-tazobactam group n=3121</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)(^{a,b})</td>
<td>52.82 ± 17.48</td>
<td>47.49 ± 15.61</td>
<td>53.28 ± 17.56</td>
<td>&lt;0.0001(^{c})</td>
</tr>
<tr>
<td>Male sex</td>
<td>1709 (50.37)</td>
<td>175 (64.34)</td>
<td>1534 (49.15)</td>
<td>&lt;0.0001(^{c})</td>
</tr>
<tr>
<td>Charlson Comorbidity Index(^a,b)</td>
<td>3.42 ± 3.62</td>
<td>2.77 ± 3.19</td>
<td>3.47 ± 3.65</td>
<td>0.0084(^d)</td>
</tr>
<tr>
<td>Baseline Cl(_{\text{Cr}}) (mL/min)(^a,b)</td>
<td>100.91 ± 42.89</td>
<td>106.9 ± 42.73</td>
<td>100.4 ± 42.87</td>
<td>0.0161(^e)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>233 (6.87)</td>
<td>15 (5.51)</td>
<td>218 (6.98)</td>
<td>0.3578(^e)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>393 (11.58)</td>
<td>51 (18.75)</td>
<td>342 (10.96)</td>
<td>0.0001(^e)</td>
</tr>
<tr>
<td>Concomitant nephrotoxins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI</td>
<td>609 (17.95)</td>
<td>63 (23.16)</td>
<td>546 (17.49)</td>
<td>0.0195(^e)</td>
</tr>
<tr>
<td>ARB</td>
<td>142 (4.19)</td>
<td>9 (3.31)</td>
<td>133 (4.26)</td>
<td>0.4518(^e)</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>28 (0.83)</td>
<td>8 (2.94)</td>
<td>20 (0.64)</td>
<td>0.0012(^f)</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>165 (4.86)</td>
<td>28 (10.29)</td>
<td>137 (4.39)</td>
<td>&lt;0.0001(^e)</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>14 (0.41)</td>
<td>3 (1.10)</td>
<td>11 (0.35)</td>
<td>0.0959(^f)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>13 (0.38)</td>
<td>1 (0.37)</td>
<td>12 (0.38)</td>
<td>1.0000(^f)</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>1 (0.03)</td>
<td>0 (0.00)</td>
<td>1 (0.03)</td>
<td>1.0000(^f)</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>679 (20.01)</td>
<td>67 (24.63)</td>
<td>612 (19.61)</td>
<td>0.0470(^e)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>365 (10.76)</td>
<td>54 (19.85)</td>
<td>311 (9.96)</td>
<td>&lt;0.0001(^e)</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>25 (0.74)</td>
<td>7 (2.57)</td>
<td>18 (0.58)</td>
<td>0.0027(^f)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>69 (2.03)</td>
<td>0 (0.00)</td>
<td>69 (2.21)</td>
<td>0.0057(^f)</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>22 (0.65)</td>
<td>4 (1.47)</td>
<td>18 (0.58)</td>
<td>0.0940(^f)</td>
</tr>
<tr>
<td>IV contrast</td>
<td>1666 (49.10)</td>
<td>163 (59.93)</td>
<td>1503 (48.16)</td>
<td>0.0002(^e)</td>
</tr>
<tr>
<td>Number of concomitant nephrotoxins</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001(^e)</td>
</tr>
<tr>
<td>0</td>
<td>895 (26.38)</td>
<td>53 (19.49)</td>
<td>842 (26.98)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1476 (43.50)</td>
<td>91 (33.46)</td>
<td>1385 (44.38)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>784 (23.11)</td>
<td>78 (28.68)</td>
<td>706 (22.62)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>203 (5.98)</td>
<td>40 (14.71)</td>
<td>163 (5.22)</td>
<td></td>
</tr>
<tr>
<td>4+</td>
<td>35 (1.03)</td>
<td>10 (3.68)</td>
<td>25 (0.80)</td>
<td></td>
</tr>
<tr>
<td>Duration of Therapy (days)(^a,b)</td>
<td>4.93 ± 3.95</td>
<td>8.46 ± 9.96</td>
<td>4.63 ± 2.67</td>
<td>&lt;0.0001(^d)</td>
</tr>
</tbody>
</table>

\(^{a}\)Mean ± Standard Deviation, \(^{b}\)Median (Interquartile Range), \(^{c}\)Student’s T-test, \(^{d}\)Wilcoxon Rank Sum Test, \(^{e}\)Chi-Square Test, \(^{f}\)Fisher’s Exact Test

Data are number (percentage) unless otherwise indicated. ACEI = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; Cl\(_{\text{Cr}}\) = creatinine clearance (adjusted Cockcroft-Gault); NSAID = non-steroidal anti-inflammatory drug; IV = intravenous.
<table>
<thead>
<tr>
<th>Study Group</th>
<th>Antibiotic</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nafcillin group</td>
<td>Nafcillin only</td>
<td>41 (15.07)</td>
</tr>
<tr>
<td></td>
<td>Nafcillin + Piperacillin-tazobactam</td>
<td>2 (0.74)</td>
</tr>
<tr>
<td></td>
<td>Nafcillin + Vancomycin</td>
<td>90 (33.09)</td>
</tr>
<tr>
<td></td>
<td>Nafcillin + Piperacillin-tazobactam + Vancomycin</td>
<td>139 (51.10)</td>
</tr>
<tr>
<td>Piperacillin-tazobactam group</td>
<td>Piperacillin-tazobactam only</td>
<td>3121 (100.00)</td>
</tr>
</tbody>
</table>

Data are number (percentage) unless otherwise indicated.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall n=3,393</th>
<th>Nafcillin group n=272</th>
<th>Piperacillin-tazobactam group n=3,121</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Kidney Injury, overall</td>
<td>294 (8.66)</td>
<td>53 (19.49)</td>
<td>241 (7.72)</td>
<td>&lt;0.0001a</td>
</tr>
<tr>
<td>Risk</td>
<td>230 (6.78)</td>
<td>38 (13.97)</td>
<td>192 (6.15)</td>
<td></td>
</tr>
<tr>
<td>Injury</td>
<td>47 (1.39)</td>
<td>10 (3.68)</td>
<td>37 (1.19)</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>17 (0.50)</td>
<td>5 (1.84)</td>
<td>12 (0.38)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3: Cumulative Incidence of Acute Kidney Injury (Unadjusted)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NAF n=41</th>
<th>NP n=2</th>
<th>NV n=90</th>
<th>NPV n=139</th>
<th>PTZ n=3121</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Kidney Injury, overall</td>
<td>9 (21.95)</td>
<td>0 (0.00)</td>
<td>16 (17.78)</td>
<td>28 (20.14)</td>
<td>241 (7.72)</td>
<td>&lt;0.0001b</td>
</tr>
<tr>
<td>Risk</td>
<td>7 (17.07)</td>
<td>0 (0.00)</td>
<td>11 (12.22)</td>
<td>20 (14.39)</td>
<td>192 (6.15)</td>
<td></td>
</tr>
<tr>
<td>Injury</td>
<td>1 (2.44)</td>
<td>0 (0.00)</td>
<td>4 (4.44)</td>
<td>5 (3.60)</td>
<td>37 (1.19)</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>1 (2.44)</td>
<td>0 (0.00)</td>
<td>1 (1.11)</td>
<td>3 (2.16)</td>
<td>12 (0.38)</td>
<td></td>
</tr>
</tbody>
</table>

Data are number (percentage) unless otherwise indicated. NAF = nafcillin only; NP = nafcillin + piperacillin-tazobactam; NV = nafcillin + vancomycin; NPV = nafcillin + piperacillin-tazobactam + vancomycin.

*aChi-Square Test  
*bFisher’s Exact Test
Table 4: Adjusted Odds Ratio for Acute Kidney Injury for Nafcillin as compared to Piperacillin-tazobactam

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>Odds Ratio (OR)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Kidney Injury, overall</td>
<td>2.002</td>
<td>1.357 - 2.953</td>
</tr>
<tr>
<td>Risk</td>
<td>1.799</td>
<td>1.162 - 2.786</td>
</tr>
<tr>
<td>Injury</td>
<td>2.246</td>
<td>0.958 - 5.264</td>
</tr>
<tr>
<td>Failure</td>
<td>2.357</td>
<td>0.685 - 8.113</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>Odds Ratio (OR)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Kidney Injury, overall</td>
<td>2.634</td>
<td>1.154 - 6.016</td>
</tr>
</tbody>
</table>

Data analyzed using logistic regression. Adjusted for age, sex, Charlson Comorbidity Index, baseline creatinine clearance, hypotension, number of concomitant nephrotoxins, and duration of therapy.
<table>
<thead>
<tr>
<th></th>
<th>Overall n=294</th>
<th>Nafcillin group n=53</th>
<th>Piperacillin-tazobactam group n=241</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to Acute Kidney Injury</strong>&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>4.93 ± 3.80 4 (4)</td>
<td>6.00 ± 5.14 5 (4)</td>
<td>4.69 ± 3.41 4 (4)</td>
<td>0.0458&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Hospital Length of Stay</strong>&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>8.00 ± 8.30 5 (6)</td>
<td>14.38 ± 12.69 10 (11)</td>
<td>7.44 ± 7.55 5 (6)</td>
<td>&lt;0.0001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>135 (3.98)</td>
<td>23 (8.46)</td>
<td>112 (3.59)</td>
<td>&lt;0.0001&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Data are number (percentage) unless otherwise indicated.
<sup>a</sup>Mean ± Standard Deviation, <sup>b</sup>Median (Interquartile Range), <sup>c</sup>Wilcoxon Rank Sum Test, <sup>d</sup>Chi-Square Test
Acknowledgements

The completion of this capstone project would not have been possible without the help of numerous faculty members, friends, family, and peers. I would especially like to express my sincere gratitude to Dr. Daniela Moga and Dr. Craig Martin for their continued mentorship and guidance throughout the years. Your patience, encouragement, and expertise are greatly appreciated. I would also like to thank Dr. Cliff Rutter for his insight and assistance with my project, and the rest of my capstone committee, Dr. Lorie Chesnut and Dr. David Mannino, for their time and feedback. Finally, I would like to thank my parents, Kishor and Priti Patel, for their endless love and support in everything I do. I owe my success to you.

I have no relevant financial or material support to disclose.

This study was exempt from IRB approval as only de-identified data were used.
Biographical Sketch

Sonali Kishor Patel is a fourth year Doctor of Pharmacy student at the University of Kentucky College of Pharmacy. She is participating in a dual degree program working towards a Master of Public Health with a concentration in epidemiology at the University of Kentucky College of Public Health. Sonali is currently employed as a pharmacy intern at Walmart Pharmacy. Professional affiliations include Rho Chi Honor Society, Kentucky Alliance of Pharmacy Students, Lambda Kappa Sigma, American Pharmacists Association, Kentucky Pharmacists Association, American Society of Health-System Pharmacists, Kentucky Society of Health-System Pharmacists, and National Community Pharmacists Association. After graduation, Sonali will be completing a Post-Graduate Year 1 pharmacy residency at Grady Memorial Hospital in Atlanta, Georgia. With interests in infectious diseases and academia, Sonali’s long-term career goal is to become an infectious diseases clinical pharmacist and adjunct faculty member.

Contact Information:

860 Wolf Hills Boulevard
Henderson, Kentucky 42420

(920) 238-7095
sonals91@gmail.com