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USING MACHINE LEARNING TO PREDICT ACUTE KIDNEY INJURIES AMONG
PATIENTS TREATED WITH EMPIRIC ANTIBIOTICS

DISSERTATION

A dissertation submitted in partial fulfillment of the requirements for the degree of
Doctor of Philosophy in the College of Pharmacy at the University of Kentucky

By

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Lexington, Kentucky

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Lexington, Kentucky

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ABSTRACT OF DISSERTATION

USING MACHINE LEARNING TO PREDICT ACUTE KIDNEY INJURIES AMONG PATIENTS TREATED WITH EMPIRIC ANTIBIOTICS

Acute kidney injury (AKI) is a significant adverse effect of many medications that leads to increased morbidity, cost, and mortality among hospitalized patients. Recent literature supports a strong link between empiric combination antimicrobial therapy and increased AKI risk. As briefly summarized below, the following chapters describe my research conducted in this area.

Chapter 1 presents and summarizes the published literature connecting combination antimicrobial therapy with increased AKI incidence. This chapter sets the specific aims I aim to achieve during my dissertation project.

Chapter 2 describes a study in which patients receiving vancomycin (VAN) in combination with piperacillin-tazobactam (TZP) or cefepime (CFP). I matched over 1,600 patients receiving both combinations and found a significantly lower incidence of AKI among patient receiving the CFP+VAN combination when controlling for confounders. The conclusion of this study is that VAN+TZP has significantly increased risk of AKI compared to CFP+VAN, confirming the results of previous literature.

Chapter 3 presents a study of patients receiving VAN in combination with meropenem (MEM) or TZP. This study included over 10,000 patients and used inverse probability of treatment weighting to conserve data for this population. After controlling for confounders, VAN+TZP was associated with significantly more AKI than VAN+MEM. This study demonstrates that MEM is clinically viable alternative to TZP in empiric antimicrobial therapy.

Chapter 4 describes a study in which patients receiving TZP or ampicillin-sulbactam (SAM) with or without VAN were analyzed for AKI incidence. The purpose of this study was to identify whether the addition of a beta-lactamase inhibitor to a beta-lactam increased the risk of AKI. This study included more than 2,400 patients receiving either agent and found that there were no differences in AKI among patients receiving SAM or TZP; however, AKI was significantly more common in the TZP group when stratified by VAN exposure. This study shows that comparisons of TZP to other beta-lactams without beta-lactamase inhibitors are valid.

Chapter 5 presents a study of almost 30,000 patients who received combination antimicrobial therapy over an 8-year period. This study demonstrates similar AKI incidence to previous literature and the studies presented in the previous chapters. Additionally, the results of the predictive models suggest that further work in this research area is needed.

The studies conducted present a clear message that patients receiving VAN+TZP are at significantly greater risk of AKI than alternative regimens for empiric coverage of infection.

KEYWORDS: Vancomycin, piperacillin-tazobactam, nephrotoxicity, supervised learning

W. Cliff Rutter

April 9, 2018

Date

USING MACHINE LEARNING TO PREDICT ACUTE KIDNEY
INJURIES AMONG PATIENTS TREATED WITH EMPIRIC ANTIBIOTICS

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*I dedicate this dissertation to my loving wife Chantal Le Rutter.
Without her support and encouragement, I would never have successfully completed this
experience.*

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Chapter 1: Systematic literature review

Background

Acute kidney injuries (AKI) are common in hospitalized patients, with approximately 20% of adult inpatients and over 65% of critically ill patients experiencing AKI. In addition to high incidence among acutely ill patients, AKI is associated with increased mortality with unadjusted estimates of 23.9% mortality associated with one episode of AKI in adults.(1) Chief among modifiable risk factors are medications, which are commonly implicated in cases of AKI. (2)

The glycopeptide antibiotic Vancomycin (VAN) is frequently implicated in AKI cases and has highly variable incidence of AKI associated with use. Estimates of VAN-associated AKI range from 1 to 42%, depending on the patient cohort studied.(3–5). Risk factors for VAN-associated AKI include: concomitant administration of other nephrotoxic agents, prolonged duration of VAN therapy, daily VAN doses of 4 g or greater, and obesity.(6) The current methicillin-resistant *Staphylococcus aureus* treatment guidelines suggest targeting higher VAN levels to account for rising minimum-inhibitory concentrations.(7)

Combination antimicrobial therapy with VAN and an antipseudomonal beta-lactam is frequently utilized as empiric therapy for acutely ill patients. Common antipseudomonal beta-lactams include piperacillin-tazobactam (TZP), cefepime (CFP), and the carbapenems, meropenem (MEM), imipenem, and doripenem. While generally considered non-nephrotoxic, systemic use of early penicillins and first-generation cephalosporins are associated with cases of acute interstitial nephritis (AIN).(8) However, reports of AIN associated with CFP are published.(9) In registration trials, TZP was not associated with significant increases in AKI and therefore, AKI does not appear in the package inserts for TZP.(10)

Recent reports suggest that combination antimicrobial therapy with VAN and TZP is associated significantly increased AKI rates when compared to TZP monotherapy and other beta-lactam/VAN combinations. This review focuses on the current literature regarding increases in AKI with beta-lactam and VAN combinations for empiric therapy.

Methods

A literature search was conducted using the PubMed database. Several queries were made with search terms including [“piperacillin”, “tazobactam”, “cefepime”, “meropenem”, “vancomycin”] and [“acute kidney injury”, “nephrotoxicity”]. English language studies of humans with available full-text articles were included in this review. Following screening of articles, additional articles were obtained from study bibliographies. Studies were separated based on comparator agents, target population, and evaluation of different IV administration modalities.

Combination therapy with Vancomycin and Piperacillin-Tazobactam compared to Monotherapy

VAN-associated nephrotoxicity is a well-characterized adverse effect of VAN therapy; however, prior to 2014, no studies had reported increased rates of AKI when combined with TZP. Table 1.1 summarizes the literature reviewed relating to VAN+TZP compared to monotherapy options.

Vancomycin combined with piperacillin-tazobactam compared to vancomycin alone

In a retrospective review of factors associated with VAN nephrotoxicity, Meaney and colleagues(11) evaluated 125 patients who received VAN for at least 3 days. Patients with underlying chronic kidney disease (CKD) and AKI on admission were excluded from the analysis. They defined AKI according to the vancomycin consensus guidelines (increase in serum creatinine [SCr] by 1.5 times baseline or by 0.5 mg/dL from baseline value).(6) Overall, they found 17.6% of patients experienced an AKI; however, when stratified by TZP administration,

patients with concomitant TZP administration were more likely to experience AKI (22.4% vs 6%; aOR 5.36, 95%CI 1.41-20.5). This study was primarily limited by small sample size and limited control for confounders of treatment selection. This was the first report of the interaction between VAN and TZP and increased AKI.

Shortly after Meaney and colleagues, Burgess and Drew(12) conducted a retrospective cohort study in which 191 patients received VAN alone or VAN+TZP for at least 48 hours and found AKI rates were significantly elevated in combination therapy patients (16.3% vs 8.1%, $p=0.041$). After controlling for confounders, VAN+TZP therapy was associated with an adjusted odds ratio (aOR) of 2.48 ($p=0.032$). The use of one-sided statistical tests and small patient enrollment are significant limitations to this study.

In a study of adult surgical patients, Davies and colleagues(13) were unable to find a significant difference in AKI incidence among patients receiving VAN+TZP, VAN monotherapy, and VAN combined with other beta-lactam agents. However, the numbers in this study included patients multiple times due to differing infection episodes and patients were able to receive different therapeutic options based on the episode.

Anderson and colleagues(14) compared adult non-critically ill patients receiving VAN+TZP or VAN alone for at least 48 hours and found combination therapy significantly increased AKI incidence (24% vs 11%, $p<0.001$; aOR 2.14 [1.26-3.66]). This study was conducted in a military hospital and had a surprisingly high mean Charlson Comorbidity index for non-critically ill patients less than 65 years of age.

Two studies examined the impact of antimicrobial stewardship interventions on AKI incidence among patients receiving VAN+TZP. Fodero and colleagues(15) found higher rates of AKI among combination therapy patients (12.8% vs 6.7%, $p=0.04$). Increased AKI odds persisted after controlling for confounders (aOR =3.21 [1.43-7.96]). Lorenz et al(16) examined

the impact of TZP restriction on AKI incidence and found significantly lower AKI incidence in the post-intervention cohort (9% vs 10%, $p=0.039$). In addition to the impact of the specific stewardship intervention, VAN+TZP had significantly higher AKI incidence throughout the study period (11.8% vs. 1.7%, $p<0.0001$). Additionally, increased duration of therapy for TZP and combination therapy were associated with increased AKI.

Combination therapy compared to piperacillin-tazobactam monotherapy

Kim et al.(17) conducted the first study of VAN+TZP with TZP as monotherapy. Patients receiving VAN+TZP had an AKI incidence of 18.8% compared to 4.0% for VAN monotherapy and 15.4% for TZP monotherapy. These results show that VAN monotherapy was associated with significantly less AKI compared to both VAN+TZP ($aOR_{VAN\ vs\ VAN+TZP} = 0.14 [0.04-0.52]$) and TZP alone ($aOR_{VAN\ vs\ TZP} = 0.15 [0.03-0.83]$). However, TZP and VAN+TZP had similar rates and adjusted odds of AKI ($aOR_{TZP\ vs\ VAN} = 0.91 [0.22-3.82]$). Low patient enrollment in the TZP arm, 36 patients compared to 101 for both VAN monotherapy and combination therapy, significantly limited the power of any analysis of TZP monotherapy.

In the largest study to date of VAN+TZP associated AKI, Rutter et al(18) demonstrated significant differences in AKI incidence between VAN+TZP (21.0%), VAN monotherapy(8.3%), and TZP monotherapy (7.8%, $p<0.0001$). After controlling for confounders, AKI odds were significantly lower in TZP and VAN monotherapy compared to VAN+TZP therapy ($aOR_{TZP\ vs\ VAN+TZP} = 0.42 [0.37-0.5]$ and $aOR_{VAN\ vs\ VAN+TZP} = 0.48 [0.41-0.57]$). Patients who received combination therapy were significantly more ill at baseline compared to either monotherapy arm; however, the observed differences in AKI incidence were consistent across varying Charlson Comorbidity Index strata.

Summary

Estimates of AKI incidence associated with VAN+TZP therapy range from 11.8% to 24.0% compared to VAN monotherapy estimates of 4% to 22% and TZP monotherapy estimates of 1.7 to 15.4% of patients. While these values are similar, comparisons across studies is difficult due to differing patient populations and AKI definitions. It is clear from the presented literature that AKI incidence is significantly increased when the combination of VAN and TZP is utilized when compared to either agent as monotherapy with only one study failing to find a significant difference between these groups.

Combination therapy with vancomycin and piperacillin-tazobactam compared to combination therapy with vancomycin and cefepime

The most common comparator for VAN+TZP in the literature to date is VAN+CFP due to the similarity in antimicrobial spectrum and clinical utility. Table 1.2 summarizes the published literature for studies comparing these two combination regimens.

Vancomycin plus piperacillin-tazobactam compared to cefepime in general hospitalized patients

Moenster and colleagues(23) first studied the differences in AKI potential between VAN+TZP and VAN+CFP in single center retrospective review of 139 diabetic patients who suffered from osteomyelitis. This study estimated that AKI occurred in 29.3% of VAN+TZP patients compared to 13.3% in VAN+CFP patients. Due to small sample size in the VAN+CFP cohort, no statistical difference could be established with the adjusted odds ratio for AKI among VAN+TZP patients reaching 3.45 [95%CI 0.96-12.4]. This study is limited by its small sample size and narrow application due to patient population examined. Additionally, no inference regarding impact of additional concomitant nephrotoxins could be made due to the exclusion of patients who received specific agents.

In a matched cohort study of 224 patients receiving VAN+TZP or VAN+CFP for at least 48 hours, Gomes et al(24) found the AKI incidence among VAN+TZP was significantly higher than those receiving VAN+CFP (34.8% vs. 12.5%; $p < 0.0001$). After matching and controlling for remaining confounders, treatment with VAN+TZP was associated with a 5.67 multiplicative increase in AKI odds when compared to VAN+CFP (95% CI 1.66-19.33).

Sutton and colleagues(25) reviewed 292 patients who received VAN from specific manufacturers for at least 48 hours. While no difference in AKI was observed between the two VAN products, investigators observed that patients receiving VAN+TZP had numerically higher rates of AKI (21.3%). In contrast, only 4.5% of patients who received CFP in addition to VAN experienced AKI. The odds of AKI were not statistically different (OR = 0.46 [0.15-1.35]) when compared. The study was not powered to investigate this finding and no attempts to control for differences between VAN+TZP and VAN+CFP patients were made. Although this study did not find a significant difference between the combination therapy options, it does assuage the concerns that different VAN products may be responsible for differing rates of AKI observed in other studies.

The largest study of VAN+TZP and VAN+CFP associated AKI was performed by Jeon et al.(26) Investigators evaluated 5,335 patients from multiple centers. In contrast to most other studies, VAN+CFP was the predominant combination therapy (3,355 patients compared to 1,980 who received VAN+TZP). AKI incidence among VAN+TZP cohort was higher than rates among VAN+CFP patients (19.6% vs. 16.3%, $p = 0.002$). Using a Cox proportional hazards model, the hazard of AKI for patients receiving VAN+TZP was significantly increased (aHR = 1.25 [1.11-1.42]). Additionally, patients with renal impairment at baseline, defined by creatinine clearance less than 60 mL/min, were no more likely to experience AKI on VAN+TZP when compared to VAN+CFP (aHR=0.81 [0.65-1.01]).

Navalkele and colleagues(27) conducted a matched retrospective study of 558 adults who received VAN+TZP or VAN+CFP. AKI incidence was significantly higher in the VAN+TZP cohort (29.0% vs. 11.1%) and adjusted hazard was significantly increased (aHR = 4.3 [2.7 – 6.7]). Due to the matched covariates in this study, inferences about impact of concomitant nephrotoxins cannot be made.

In a prospective multicenter observational study, Mullins and colleagues compared AKI rates in patients who received VAN+TZP to those who received VAN+CFP or MEM for at least 72 hours. Among the cohort receiving VAN+TZP the incidence of AKI was 29.8% compared to 8.8% among the patients receiving VAN+CFP/MEM ($p < 0.001$); however, incidence among the patients receiving VAN+CFP was only 5.9% ($p < 0.001$ for comparison to VAN+TZP). Investigators only completed bivariable statistical analysis and report a crude odds ratio of 6.6 [2.8-15.8] for AKI between VAN+TZP and VAN+CFP/MEM. Additionally, VAN troughs greater than 30 mg/L were significantly associated with AKI; however, the timing of VAN trough in relation to AKI was not clear and this may represent an effect of AKI not a cause. This study was limited by the choice to only complete bivariable analysis and small sample size.

Vancomycin and piperacillin-tazobactam compared to vancomycin and cefepime in special populations

Hammond and colleagues(28) conducted the only published study of AKI incidence among combination therapy options in the critically ill population to date. Due to the severity of illness among the overall cohort, AKI incidence higher than previous studies; however, no difference in rates were noted between patients receiving VAN+TZP and those receiving VAN+CFP (32.7% vs. 28.8%, $p = 0.647$). This study was significantly limited by small sample size of only 122 patients.

Clemmons et al(29) conducted a retrospective cohort evaluation of adult patients undergoing hematopoietic cell transplantation (HCT) who received VAN+TZP or VAN+CFP. AKI incidence among VAN+TZP was significantly higher than the rate found in VAN+CFP (68% vs. 27%, $p < 0.001$). After controlling for significant confounders of AKI among the cohort, VAN+TZP was associated with a 5.16 multiplicative increase in adjusted odds of AKI compared to VAN+CFP (95% CI 2.53-10.5). After stratification by allogeneic and autologous HCT, the association with AKI remained for VAN+TZP.

Summary

Estimates of AKI for VAN+TZP in the previous studies ranged from 19.7% to 34.8% in the general population compared to 4.5% to 16.3% for VAN+CFP. AKI incidence is significantly higher among patients with increased severity of illness for both VAN+TZP and VAN+CFP.

Vancomycin and piperacillin-tazobactam compared to other Gram-negative therapy options in combination with vancomycin

The study by Davies and colleagues was briefly presented in the VAN+TZP compared to monotherapy section of this review; however, this study presents the first attempt at identifying if AKI incidence was significantly different between other VAN+TZP and other beta-lactam agents. They estimate the AKI incidence of VAN+TZP to be 21% compared to 20% in VAN+CFP or MEM treated patients. They did not examine a group-wise comparison and report a p-value of 0.89 for the Kruskal-Wallis test for the three groups in their study. This suggest there is no difference in AKI incidence; however, using infection episodes as the unit of observation may skew the results.

In a prospective observational study, Peyko and colleagues(31) evaluated 85 patients receiving either VAN+TZP or VAN+CFP or MEM. AKI incidence was significantly higher amongst the VAN+TZP cohort (37.3% vs. 7.7%, $p = 0.005$). This study did not breakdown results

between CFP and MEM combination cohorts. The primary limitation of this study was the differences in severity of illness and potential for increased dosing intensity among the VAN+TZP cohort. While there was no measure for severity of illness included in the publication, more patients in the VAN+CFP/MEM had less severe infections compared to the VAN+TZP cohort. Increased infection severity may have increased the observed difference in AKI incidence in this study.

In a study by Al Yami(32), AKI incidence in VAN+TZP patients was estimated as 7.4% compared to 5.3% in VAN+MEM patients ($p=0.4$). This study is the only study to directly compare combination therapy with TZP to combination therapy with MEM only. However, AKI rates are far below reports from prior studies which limits the generalizability to a wider patient population. Other limitations include small sample size and no control of other nephrotoxic confounders.

Finally, Mullins et al(30) included patients who received VAN+MEM in their study. Investigators were unable to find a statistically meaningful difference between VAN+TZP (29.8%) and VAN+MEM (14.9%; $p=0.54$). This study has several limitations, as discussed previously, however, a specific limitation of this analysis is low patient enrollment in the VAN+MEM cohort ($n=47$ compared to 94 for VAN+TZP).

Summary

Limited data comparing VAN+TZP to non-CFP beta-lactam agents exist; however, AKI incidence among VAN+TZP cohorts (21% to 37.3%) are similar to previous literature. AKI incidence among VAN combined with other beta-lactams ranges from 7.7% to 20%. Further study of alternative empiric combination therapy is warranted.

Impact of beta-lactam infusion method on AKI

Several studies have examined the rate of infusion of beta-lactam agents to determine if an association with increased AKI exists. McCormick and colleagues(33) published the first study on this topic. They included 200 patients who received TZP by either extended infusion (EI) or bolus infusion (BI) for at least 48 hours. They found AKI incidence of 9.5% overall and no statistical difference between EI and BI (9% vs 11%, $p=0.637$). The investigators did not specifically control for VAN exposure and excluded all patients who received a non-TZP beta-lactam.

Karino et al(34) conducted a single-center retrospective review of 320 patients who received TZP as either EI or BI for at least 48 hours. In contrast to the study by McCormick and colleagues, investigators specifically included patients who received concomitant VAN. Estimates of AKI incidence between both EI and BI groups were not significantly different (32.5% vs. 33.1%, $p=1$). These rates of AKI are relatively high compared to previous studies; however, the majority of patients in both groups received concomitant nephrotoxins, which were associated with increased AKI odds in multivariable regression analysis.

In a matched cohort study, Cotner et al(35) examined 2,390 patients who received at least 48 hours of TZP, CFP, or MEM as bolus or extended infusion. Importantly, not all patients received VAN in combination with beta-lactams. AKI incidence was similar between infusion methodologies (EI 21.6% vs. 18.6% for BI, $p=0.104$). In multivariable regression, infusion method did not have a statistical impact on AKI odds (aOR 1.07, 95%CI 0.83-1.39); however, when compared to CFP, TZP administration significantly increased AKI odds (aOR 1.95 [1.50-2.52]). The addition of VAN was associated with a 1.6 time multiplicative increase in AKI odds (95% CI 1.16-2.21). Other nephrotoxins associated with significant increases in AKI odds in

multivariable regression included: aminoglycosides, amphotericin b, calcineurin inhibitors, loop diuretics, non-steroidal anti-inflammatory drugs, and vasopressors.

Mousavi and colleagues(36) conducted a retrospective review of 280 patients in a 1:1 ratio of BI to EI who received VAN+TZP for at least 48 hours. Investigators mitigated the potential for severity of illness to confound results by matching patients based on level of care (IE. ICU patients who received EI were matched to ICU patients who received BI). This was primarily in response to a treatment algorithm that prevailed in the study institution during the study period. In total, 17.5% of patients experienced an AKI with no significant differences between EI and BI cohorts (17.9% vs 17.1%, $p>0.99$).

Summary

AKI incidence among patients in studies of beta-lactam infusion methodology were similar to those reported in other studies. Limited data are published in this arena; however, it appears that infusion strategy does not influence AKI incidence in an appreciable way.

Vancomycin and piperacillin-tazobactam associated AKI in the pediatric population

While the majority of data exist in the adult population, significant research has been conducted in pediatric patients. Pratt, et al published a case series of four pediatric cases of AKI associated with TZP administration in patients with underlying oncologic conditions.(37) Interestingly, VAN was utilized concomitantly in each case; however, interstitial nephritis was confirmed in 50% of cases, suggesting beta-lactam associated AKI.

In 2015, Knoderer and colleagues(38) published the first cohort study of AKI incidence in pediatric patients receiving VAN+TZP. The primary objective was to establish risk factors for late onset AKI in VAN therapy; therefore, inclusion was limited to patients who received VAN therapy for at least 8 days. In total, 167 patients were included for analysis, of which 69 received VAN+TZP compared to 98 who received VAN alone. AKI occurred in 18.8% of patients

receiving VAN+TZP compared to 8.2% in VAN alone ($p=0.06$). In addition to small sample size and limited power, the AKI incidence in VAN+TZP may be confounded due to significantly higher rates of concomitant amphotericin B administration.

McQueen and Clark(39) published the first directed analysis of VAN+TZP compared to VAN monotherapy in pediatric patients. Overall, 185 patients were included in this study and AKI occurred in 23.6% of the VAN+TZP cohort and 3.8% in the VAN alone cohort ($p=0.0001$). Investigators only completed bivariable analysis and therefore have no control for known confounders present in the patient population. Additionally, rather than selecting an equal population, the VAN monotherapy group was selected randomly from a larger cohort.

Abouelkheir, et al(40) published a large case report of pediatric patients less than 14 years of age who received VAN for at least 48 hours. Of 132 patients, 8 experienced AKI related to study drug administration. This evaluation is unique in the use of validated methods to associated AKI with VAN administration. Using the World Health Organization Uppsala Monitoring Centre system for evaluation of case causality, 50% of AKI cases were rated as having certain causality. Of the 38 patients who received VAN+TZP, 21.0% experienced AKI compared to 2.1% of the 94 patients who received VAN alone ($p=0.0007$). These estimates are extrapolated from the data provided in the manuscript and represent unadjusted incidence.

Downes and colleagues(41) conducted the largest study to date in pediatric patients. They included 1,915 patients from multiple centers who received VAN in combination with an anti-pseudomonal beta-lactam. Patients in the VAN+TZP cohort experienced AKI significantly more frequently compared to VAN in combination with other anti-pseudomonal beta-lactams (11.7% vs. 4.4%, $p<0.001$). While this study is robust, investigators only included patients who received study agents within 48 hours of admission and limited the analysis to AKI that occurred within 7 days of admission, which may limit applicability of these findings to treatment of nosocomial infections or long courses of antibiotics.

While all the previous studies included all patients, Holsen et al(42) compared patients admitted to the pediatric intensive care unit who received VAN+TZP or VAN in combination with ceftriaxone. In total, 93 patients met inclusion criteria with the majority (58) receiving VAN+TZP. AKI was significantly more common in VAN+TZP compared to VAN+ceftriaxone (25.9% vs. 8.6%, $p=0.041$). This finding was consistent in multivariable regression analysis (aOR 4.55 [1.11-18.7]). Limitations of this study are primarily related to the lack of control for severity of illness differences between groups. TZP is typically utilized for empiric therapy or for severe infections, while ceftriaxone lacks similar indications and antimicrobial spectrum.

Summary

Studies of pediatric patients estimate the AKI incidence associated with VAN+TZP therapy ranges from 11.7% to 23.9% of patients. VAN+TZP patients consistently experience higher rates of AKI than comparator groups. More research in critically ill pediatric patients is warranted.

Further questions and aims to be addressed

While literature in this area continues to evolve, there are still several opportunities to improve upon what has been published. There is significant support for an interaction between VAN and TZP that increases AKI potential when compared to either agent as monotherapy.

Aim 1: Compare AKI incidence rate among patients treated with VAN+TZP and VAN+CFP in a study large enough to robustly control for confounders

Due to similarity in antimicrobial spectrum and clinical utility, TZP is often compared to CFP and many studies have shown significant AKI increases with VAN+TZP. However, many of these studies were small single center studies with limited power to control for other confounders. We conducted a large robust retrospective study to determine AKI incidence and identify potential confounders.

Aim 2: Determine if beta-lactamase inhibitor influences AKI seen with TZP

Many of the studies discussed previously took cues from comparative effectiveness research and compared agents with similar indications and spectrum of activity. However, one major difference between TZP and the comparators used is the presence of a beta-lactamase inhibitor in combination with a beta-lactam agent. It is possible that the addition of this second beta-lactam-like agent contributes to the increased AKI potential noted with TZP. Unfortunately, ticarcillin-clavulanate, an agent with similar spectrum and indication to TZP, is no longer widely used. Another agent that is widely used, but lacks the indication for certain severe infections is ampicillin-sulbactam. We conducted a large retrospective review of TZP compared to ampicillin-sulbactam, with and without concomitant VAN to identify differences in AKI.

Aim 3: Compare AKI incidence between VAN+TZP and VAN+MEM

While there have been studies that include patients who received MEM in combination with VAN, many grouped MEM with other beta-lactam agents to increase sample size and statistical power. This may lead to bias in AKI incidence as MEM is typically reserved for patients with multidrug resistant infections, who typically have higher comorbidity than those without MDR organisms. These studies also suffered from small sample sizes. We conducted a large study and weighted patients according to their probability of receiving either treatment agent.

Aim 4: Can machine learning methods accurately predict AKI occurrence in patients treated with empiric combination antimicrobial therapy?

Previous studies have relied on relatively small sample sizes to identify factors that are associated with increased AKI incidence. We leveraged our electronic data warehouse to develop sophisticated supervised learning algorithms to predict AKI occurrence at the patient level.

Furthermore, we framed the predictive models as a clinical decision support tool to demonstrate utility in clinical practice.

Table 1.1: Studies of AKI incidence with vancomycin combined with piperacillin-tazobactam compared to either agent as monotherapy

| Study | Design | Patient population | Groups | N | AKI | Findings |
|---------------------------|---|--|-----------------------|--|-----|--|
| Meaney, et al, 2014 (11) | Retrospective Single center Observational | <ul style="list-style-type: none"> • Adult internal medicine patients who received VAN ≥ 72h • Excluded: AKI on admit or CKD, SCR > 1.4/5 (Female/Male) | VAN | Total: 125 VAN: 67 VAN+TZP : 58 | (6) | AKI Rate <ul style="list-style-type: none"> • VAN+TZP: 22.4% • VAN: 6.0% • aOR: 5.36 [1.41-20.5] |
| Burgess, et al, 2014 (12) | Retrospective Single center Observational | <ul style="list-style-type: none"> • Adult inpatients receiving VAN or VAN+TZP for ≥ 48 hrs, 4 SCr levels • Excluded: SCr >1.5, CrCl <30, RRT, recent AKI, incomplete data | VAN VAN+TZP | Total: 191 VAN: 99 VAN+TZP : 92 | (6) | AKI rate: <ul style="list-style-type: none"> • VAN+TZP: 16.3% • VAN: 8.1% • aOR 2.48 |
| Kim, et al 2015 (17) | Retrospective Single center Observational | <ul style="list-style-type: none"> • Adult noncritically ill inpatients who received VAN or TZP for ≥ 48h • Excluded: RRT | VAN+TZP VAN TZP | Total: 238 VAN+TZP : 101 VAN: 101 TZP: 36 | (6) | AKI rate <ul style="list-style-type: none"> • VAN+TZP: 18.8% • VAN: 4.0% • TZP: 15.4% • aOR_{VAN:VAN+TZP} 0.14 [0.04-0.52] • aOR_{VAN:TZP} 0.15 [0.03-0.83] |

Table 1.1 (continued)

| | | | | | | |
|-------------------------|---|---|-----------------------------|--|-------------|---|
| Davies, et al 2016 (13) | Retrospective Single Center Observational | <ul style="list-style-type: none"> •Adult surgical patients •Excluded: RRT prior to VAN | VAN+TZP VAN+Other VAN | Total: 1007 VAN+TZP :372 V-Other: 333 VAN: 302 | (6) | AKI rate: <ul style="list-style-type: none"> •VAN+TZP: 21.0% •VAN+other: 20% •VAN: 22 % •KW p-value = 0.89 |
| Fodero, et al 2016 (15) | Retrospective Single center Observational Pre/post ASP intervention | <ul style="list-style-type: none"> •Adult inpatients who received VAN for ≥ 48 hrs and had ≥ 1 VTr within 96 hrs, Scr<2 •Excluded: IV contrast within (\pm) 7 days of antibiotic initiation, Concurrent vasopressors, tacrolimus/cyclosporin, amphotericin, nephrology consult in 30 days prior to abx, if on hemodialysis | Pre-ASP Post-ASP | Total: 453 Pre: 226 Post: 227 VAN+TZP : 288 VAN: 165 | (19) (6) | AKI rate <ul style="list-style-type: none"> •VAN+TZP: 12.85% •TZP: 6.67% •p-value = 0.04 •aOR_{TZP} = 3.21 [1.43-7.96] |

Table 1.1 (continued)

| | | | | | | |
|---------------------------|--|--|--------------------------|---|------|--|
| Lorenz et al, 2016 (16) | Retrospective Observational Single center Pre-post study | <ul style="list-style-type: none"> •Adults who received TZP for at least 24 h with CrCl \geq39 | Pre Post TZP restriction | Total 242 Pre 120 Post 122 VAN+TZP 186 TZP 56 | (6) | AKI rate <ul style="list-style-type: none"> •Pre – 10% •Post – 9% •p=0.039 •VAN+TZP 11.8% •TZP 1.7% •p<0.0001 |
| Anderson et al, 2017 (14) | Retrospective Observational Single Center | <ul style="list-style-type: none"> •Non-critically ill adults who received VAN or VAN+TZP for \geq48h •Excluded for SCr > 1.5, RRT, pregnancy, or ICU | VAN+TZP VAN | Total 678 VAN+TZP 202 VAN 253 | (20) | AKI rates <ul style="list-style-type: none"> •VAN+TZP 24% •VAN 11% •p<0.001 •aOR 2.14 [1.26-3.66] |
| Rutter, et al 2017 (18) | Retrospective Single center Observational | <ul style="list-style-type: none"> •Adult inpatients who received VAN, TZP, VAN+TZP for \geq48 hrs (and 48hrs overlap for combo) •Excluded: PMH of CKD stage III +, history of hemodialysis, pregnancy or breastfeeding | VAN+TZP VAN TZP | Total: 11,650 VAN+TZP : 5497 VAN: 3,055 TZP: 3,098 | (19) | AKI rate <ul style="list-style-type: none"> •VAN+TZP: 21.0% •VAN: 8.3% •TZP 7.8% •aOR_{V:VAN+TZP} = 0.48 [0.41-0.57] •aOR_{P:VAN+TZP} = 0.42 [0.37-0.5] |

Footnote: (6) – vancomycin consensus guidelines AKI definitions; (19) – RIFLE guidelines AKI definitions; (20) – Acute kidney injury network AKI definitions; (21) – KDIGO AKI guidelines; (22) – modified RIFLE for pediatrics; aHR – adjusted Hazard ratio; AKI – acute kidney injury; ANC – absolute neutrophil count; aOR – adjusted Odds ratio; BUN – blood urea nitrogen; CF – cystic fibrosis; CFP – cefepime; CKD – chronic kidney disease; CrCl – creatinine clearance; CRO – ceftriaxone; ECMO – extracorporeal membrane oxygenation; ESRD – end-stage renal disease; HCT – hematopoietic cell transplant; KDOQI - Kidney Disease Outcomes Quality Initiative; KW – Kruskal-Wallis test; MEM – meropenem; N – number; OR – odds ratio; PICU – pediatric intensive care unit; PMH – past medical history; RRT – renal replacement therapy; SCr – serum creatinine; TZP – piperacillin/tazobactam; VAN – vancomycin; VTr – vancomycin trough level.

Table 1.2: Studies comparing AKI incidence between vancomycin combined with piperacillin-tazobactam and vancomycin combined with cefepime

| Study | Design | Patient Population | Groups | N | AKI | Findings |
|-------------------------|---|--|--------------------|--|------|--|
| Gomes, et al, 2014 (24) | Retrospective Single center Observational Matched cohort | <ul style="list-style-type: none"> • Adult inpatients who received VAN+TZP/VAN+CFP for ≥ 48 h, had SCr within 24 hrs of admission, had at least 1 VTr • Excluded: RRT, PMH, CKD, CrCl < 60, pregnancy, incarceration, treatment with investigational drugs, more than one dose of intermittent TZP, meningitis, febrile neutropenia | VAN+TZP VAN+CFP | Total: 224 VAN+TZP : 112 VAN+CFP : 112 | (20) | AKI rate: <ul style="list-style-type: none"> • VAN+TZP: 34.8% • VAN+CFP: 12.5% • OR: 5.67 [1.66-19.33] |

Table 1.2 (continued)

| | | | | | | |
|-----------------------------------|--|--|----------------------------|--|------------|---|
| <p>Moenster, et al, 2014.(23)</p> | <p>Retrospective Single center Observational</p> | <ul style="list-style-type: none"> •Adult diabetic patients with osteomyelitis who received VAN+TZP/VAN+CFP for ≥ 72 h •Excluded: CrCl <40, BUN/SC R >20, ANC < 500, received IV acyclovir, amphotericin b, aminoglycoside, or vasopressor within 48 h of antibiotics | <p>VAN+TZP VAN+CFP</p> | <p>Total: 139 VAN+TZP : 109 VAN+CFP : 30</p> | <p>(6)</p> | <p>AKI rate: •VAN+TZP: 29.3% •VAN+CFP: 13.3% •aOR: 3.45 [0.96-12.4]</p> |
|-----------------------------------|--|--|----------------------------|--|------------|---|

Table 1.2 (continued)

| | | | | | | |
|--------------------------------|---|---|-----------------------------------|--|---------------|---|
| <p>Sutton, et al 2015 (25)</p> | <p>Retrospective Single center Observational Matched cohort</p> | <ul style="list-style-type: none"> •Adults who received VAN for ≥ 48 hrs, who received only 1 product (hospira v Pfizer) as defined by date of administration, at least 2 SCr values •Excluded for elevated SCr from baseline, received RRT | <p>Hospira VAN Pfizer VAN</p> | <p>Total 292 Hospira 146 Pfizer 146 VAN+TZP :108 VAN+CFP : 66</p> | <p>(6,19)</p> | <p>AKI rate •VAN+TZP:21.3 % •VAN+CFP: 4.5% •OR = 0.46 [0.15-1.35]</p> |
|--------------------------------|---|---|-----------------------------------|--|---------------|---|

Table 1.2 (continued)

| | | | | | | |
|---------------------------|---|--|--------------------|--|------|--|
| Hammond, et al, 2016 (28) | Retrospective Single center Observational | <ul style="list-style-type: none"> •Adult critically ill patients who received VAN+TZP/CFP for 48 hrs •Excluded: RRT at antibiotic initiation, received both CFP/TZP, CrCl <60, PMH kidney disease, Multiple myeloma, febrile neutropenia | VAN+TZP VAN+CFP | Total: 122 VAN+TZP : 49 VAN+CFP : 73 | (20) | AKI rate: <ul style="list-style-type: none"> •VAN+TZP: 32.7% •VAN+CFP: 28.8% •p=0.647 |
| Clemmons et al 2017(29) | Retrospective Observational Single center | <ul style="list-style-type: none"> •Adult HCT patients who received VAN+TZP or VAN+CFP | VAN+CFP VAN+TZP | Total: 170 VAN+CFP : 114 VAN+TZP: 56 | (21) | AKI rate <ul style="list-style-type: none"> •VAN+TZP 68% •VAN+CFP 27% •p<0.001 •aOR 5.16 [2.53-10.5] |

Table 1.2 (continued)

| | | | | | | |
|------------------------------------|--|---|----------------------------------|---|------------------|--|
| <p>Jeon et al, 2017 (26)</p> | <p>Retrospective Observational Multicenter</p> | <ul style="list-style-type: none"> • Adults w/3 days of VAN in combination with TZP or CFP • Excluded for AKI on admit, baseline SCr>4, ESRD, blood loss > 6 units, received both drugs | <p>VAN+TZP VAN+CFP</p> | <p>Total: 5,335 VAN+TZP : 1,980 VAN+CFP : 3,355</p> | <p>(21)</p> | <p>AKI rate</p> <ul style="list-style-type: none"> • VAN+TZP 19.65% • VAN+CFP 16.27% • p=0.002* • aHR 1.25 [1.11-1.42] |
| <p>Navalkele, et al, 2017 (27)</p> | <p>Retrospective Single center Observational</p> | <ul style="list-style-type: none"> • Adult inpatients who received VAN+CFP or VAN+TZP for ≥48h • Excluded: baseline SCr >1.2, RRT | <p>VAN+TZP VAN+CFP s</p> | <p>Total: 558 VAN+TZP : 279 VAN+CFP : 279</p> | <p>(6,19,20)</p> | <p>AKI rate (RIFLE)</p> <ul style="list-style-type: none"> • VAN+TZP: 29.0% • VAN+CFP: 11.1% • aHR = 4.3 [2.7-6.7] |

Table 1.2 (continued)

| | | | | | | |
|---------------------------|---|--|------------------------------|--|--|--|
| Mullins, et al, 2018.(30) | Prospective Multicenter 4 centers Observational | <ul style="list-style-type: none"> •Adults who received \geq 72 hrs of VAN, TZP, MEM, or CFP with at least 48 hrs of overlap •Excluded for CKD (KDOQI stage 3+), SCR \geq1.5, AKI prior to initiation of antibiotics, VAN trough < 10 mcg/mL, received study drug prior to inclusion, suffered cardiac arrest prior to initiation of antibiotics, no VAN concentrations | VAN+TZP VAN+CFP or MEM | Total: 242 VAN+TZP T: 94 VAN+CFP /MEM: 148 CFP: 101 MEM: 47 | \geq 1.5x increase in SCR within 7 days of starting antibiotic | <p>AKI Rate</p> <ul style="list-style-type: none"> •VAN+TZP: 29.8% •VAN+CFP/MEM: 8.8% (p<0.001) •VAN+CFP: 5.9% (p<0.001) •VAN+MEM: 14.9% (p=0.054) <p>Odds Ratios:</p> <ul style="list-style-type: none"> •VAN+TZP vs VAN+CFP/M: 6.65 [2.79-15.84] •Loop diuretics: 3.27 [1.42-7.53] •Vasopressors: 5.04 [1.66-15.35] •VTr > 30: 13.33 [3.13-56.77] |
|---------------------------|---|--|------------------------------|--|--|--|

Footnote: (6) – vancomycin consensus guidelines AKI definitions; (19) – RIFLE guidelines AKI definitions; (20) – Acute kidney injury network AKI definitions; (21) – KDIGO AKI guidelines; (22) – modified RIFLE for pediatrics; aHR – adjusted Hazard ratio; AKI – acute kidney injury; ANC – absolute neutrophil count; aOR – adjusted Odds ratio; BUN – blood urea nitrogen; CF – cystic fibrosis; CFP – cefepime; CKD – chronic kidney disease; CrCl – creatinine clearance;

CRO – ceftriaxone; ECMO – extracorporeal membrane oxygenation; ESRD – end-stage renal disease; HCT – hematopoietic cell transplant; KDOQI - Kidney Disease Outcomes Quality Initiative; KW – Kruskal-Wallis test; MEM – meropenem; N – number; OR – odds ratio; PICU – pediatric intensive care unit; PMH – past medical history; RRT – renal replacement therapy; SCr – serum creatinine; TZP – piperacillin/tazobactam; VAN – vancomycin; VTr – vancomycin trough level.

Table 1.3: Studies comparing AKI incidence between vancomycin combined with piperacillin-tazobactam and vancomycin with other gram-negative alternatives

| Study | Design | Patient Population | Groups | N | AKI | Findings |
|-------------------------|---|---|-----------------------------|---|------|--|
| Davies, et al 2016 (13) | Retrospective Single Center Observational | <ul style="list-style-type: none"> • Adult surgical patients • Excluded: RRT prior to VAN | VAN+TZP VAN+Other VAN | Total: 1007 VAN+TZP: 372 V-Other: 333 VAN: 302 | (6) | AKI rate: <ul style="list-style-type: none"> • VAN+TZP: 21.0% • VAN+other: 20% • VAN: 22 % • KW p-value = 0.89 |
| Peyko et al 2017 (31) | Prospective Observational Single center | <ul style="list-style-type: none"> • Adults who received TZP or CFP or MEM for at least 72 hrs with a steady state VTr • Excluded pregnancy, history of allergy to beta-lactam, RRT prior to abx, baseline SCR > 2.5, missing lab data | VAN+TZP VAN+Other | Total: 85 VAN+TZP: 59 VAN+Other: 26 | (21) | AKI rate <ul style="list-style-type: none"> • VAN+TZP: 37.3% • VAN+Other: 7.7% • p=0.005 |

Table 1.3 (continued)

| | | | | | | |
|---------------------------|---|---|---------------------------|---|--|---|
| Al Yami MS 2017 (32) | Retrospective Observational Single Center | <ul style="list-style-type: none"> •Adults who received VAN+TZP or VAN+MEM for ≥ 48 hrs w/baseline SCr •Excluded: RRT, PMH of renal disease | VAN+TZP VAN+MEM | Total: 183 VAN+TZP : 108 VAN+MEM: 75 | (21) | AKI rate <ul style="list-style-type: none"> •VAN+TZP: 7.4% •VAN+MEM: 5.3% •p=0.4 |
| Mullins, et al, 2018.(30) | Prospective Multicenter 4 centers Observational | <ul style="list-style-type: none"> •Adults who received ≥ 72 hrs of VAN, TZP, MEM, or CFP with at least 48 hrs of overlap •See table 1.2 for exclusions | VAN+TZP VAN+CFP or MEM | Total: 242 VAN+TZP T: 94 VAN+CFP /MEM: 148 CFP: 101 MEM: 47 | $\geq 1.5x$ increase in SCR within 7 days of starting antibiotic | AKI Rate <ul style="list-style-type: none"> •VAN+TZP: 29.8% •VAN+CFP/MEM: 8.8% (p<0.001) •VAN+MEM: 14.9% (p=0.054) •VAN+TZP vs VAN+CFP/MEM: OR = 6.65 [2.79-15.84] |

Footnote: (6) – vancomycin consensus guidelines AKI definitions; (19) – RIFLE guidelines AKI definitions; (20) – Acute kidney injury network AKI definitions; (21) – KDIGO AKI guidelines; (22) – modified RIFLE for pediatrics; aHR – adjusted Hazard ratio; AKI – acute kidney injury; ANC – absolute neutrophil count; aOR – adjusted Odds ratio; BUN – blood urea nitrogen; CF – cystic fibrosis; CFP – cefepime; CKD – chronic kidney disease; CrCl – creatinine clearance; CRO – ceftriaxone; ECMO – extracorporeal membrane oxygenation; ESRD – end-stage renal disease; HCT – hematopoietic cell transplant; KDOQI - Kidney Disease Outcomes Quality Initiative; KW – Kruskal-Wallis test; MEM – meropenem; N – number; OR – odds ratio; PICU – pediatric intensive care unit; PMH – past medical history; RRT – renal replacement therapy; SCR – serum creatinine; TZP – piperacillin/tazobactam; VAN – vancomycin; VTr – vancomycin trough level.

Table 1.4: Studies of AKI incidence based on beta-lactam infusion method

| Study | Design | Patient Population | Groups | N | AKI | Findings |
|----------------------------|--|--|---------------------------|--------------------------------------|----------------------|--|
| McCor mick, et al 2015(33) | Retrospective Single Center Observational | <ul style="list-style-type: none"> • Adult patients who received TZP for at least 3 doses and admitted for 48 hrs • Excluded: SCr>4, pregnancy, penicillin allergy, concomitant beta-lactam use | TZP EI vs BI | Total: 200 EI: 100 BI: 100 | ↑2xSCr or ↑0.5 mg/dL | AKI rate <ul style="list-style-type: none"> • Overall: 9.5% • EI: 9% • BI: 11% • p = 0.637 |
| Karino, et al 2016(34) | Retrospective Single Center Observational | <ul style="list-style-type: none"> • Adult patients who received VAN+TZP for ≥48h • Excluded: RRT or SCr >1.2 | VAN+TZP EI vs BI | Total: 320 EI: 160 BI: 160 | (6,19,20) | AKI rate (RIFLE) <ul style="list-style-type: none"> • EI: 32.5% • BI: 33.1% • p=1 |
| Cotner, et al, 2017.(35) | Retrospective Single center Observational Matched cohort | <ul style="list-style-type: none"> • Adults who received ≥48 hrs of MEM, TZP, or CFP • Excluded CKD (ICD9 codes), preexisting AKI (CrCl<30), pregnancy, CF, missing lab values | MEM, CFP, TZP EI vs BI | Total: 2,390 EI: 690 BI: 1,700 | (19) | AKI Rate <ul style="list-style-type: none"> • EI: 21.6% • BI: 18.6% • p=0.104 <p>TZP vs CFP aOR 1.95 [1.5-2.52]</p> |

Table 1.4 (continued)

| | | | | | | |
|-------------------------|---|--|---------------------|----------------------------------|------|---|
| Mousavi, et al 2017(36) | Retrospective Single center Observational | <ul style="list-style-type: none"> • Adult patients who received VAN+TZP for at least 48 h in combo, had 1 VTr, and had SCr, ICU matched 1:1 for EI to ICU • Excluded: concomitant nephrotoxins, CrCl<40, RRT, switched from EI to BI | VAN+TZP EI vs BI | Total: 280 EI: 140 BI: 140 | (19) | AKI rate <ul style="list-style-type: none"> • 17.5% overall • EI: 17.9% • BI: 17.1% • p>0.99 |
|-------------------------|---|--|---------------------|----------------------------------|------|---|

Footnote: (6) – vancomycin consensus guidelines AKI definitions; (19) – RIFLE guidelines AKI definitions; (20) – Acute kidney injury network AKI definitions; (21) – KDIGO AKI guidelines; (22) – modified RIFLE for pediatrics; aHR – adjusted Hazard ratio; AKI – acute kidney injury; ANC – absolute neutrophil count; aOR – adjusted Odds ratio; BUN – blood urea nitrogen; CF – cystic fibrosis; CFP – cefepime; CKD – chronic kidney disease; CrCl – creatinine clearance; CRO – ceftriaxone; ECMO – extracorporeal membrane oxygenation; ESRD – end-stage renal disease; HCT – hematopoietic cell transplant; KDOQI - Kidney Disease Outcomes Quality Initiative; KW – Kruskal-Wallis test; MEM – meropenem; N – number; OR – odds ratio; PICU – pediatric intensive care unit; PMH – past medical history; RRT – renal replacement therapy; SCr – serum creatinine; TZP – piperacillin/tazobactam; VAN – vancomycin; VTr – vancomycin trough level.

Table 1.5: Studies of AKI associated with vancomycin and piperacillin-tazobactam therapy

| Study | Design | Patient Population | Groups | N | AKI | Findings |
|------------------------------|--|---|--------------------|--|--|---|
| Knoderer, et al, 2015 (38) | Retrospective Observational Single center | <ul style="list-style-type: none"> •Patients 30 days to 17 years old who received VAN for ≥ 8 days •Excluded for AKI within 7 days of starting VAN, elevated baseline SCr, CF | Late-AKI No AKI | Total 167 AKI 21 No AKI 146 VAN+TZP: 69 VAN: 98 | (22) | AKI rate <ul style="list-style-type: none"> •VAN+TZ P: 18.8% •VAN: 8.2% •p=0.06 •OR: 2.77 [0.97-7.9] |
| McQueen et al 2016 (39) | Retrospective Observational Single center | <ul style="list-style-type: none"> •Patients < 19 yo who received VAN or VAN+TZP for ≥ 48 hrs. •Excluded for missing SCr/BUN at baseline or follow up | VAN+TZP VAN | Total 185 VAN+TZP: 106 VAN: 79 | $\uparrow 2 \times$ SCr or $\uparrow 0.5$ mg/dL from baseline on at least 2 readings | AKI rates <ul style="list-style-type: none"> •VAN+TZ P: 23.6% •VAN: 3.8% •p=0.0001 |
| Abouelkheir et al, 2017 (40) | Retrospective Observational Single center Case study | <ul style="list-style-type: none"> •Patients 0-14 years old, who received VAN ≥ 48 hrs | VAN+TZP VAN | Total 132 VAN+TZP: 38 VAN: 94 | (22) | AKI rate <ul style="list-style-type: none"> •VAN+TZ P: 21.0% •VAN: 2.1% •p=0.0007 |
| Downes et al, 2017(41) | Retrospective Observational Multicenter | <ul style="list-style-type: none"> •Pediatrics 6 months to 18 years who received VAN + antipseudomonal beta-lactam •Excluded renal disease (icd9), dialysis, ECMO, admitted for at least 3 days, elevated SCr at baseline, AKI within 48 hrs of admission | VAN+TZP V-other | Total 1,915 AKI: 157 No AKI: 1,758 VAN+TZP: 1,009 VAN+Other: 906 | (21) | AKI rates <ul style="list-style-type: none"> •VAN+TZ P: 11.7% •V+Other: 4.4% •p<0.001 •aOR = 3.4 [2.26-5.14] |

Table 1.5 (continued)

| | | | | | | |
|------------------------|---|--|----------------------------|--------------------------------------|------|---|
| Holsen et al, 2017(42) | Retrospective Observational Single center | <ul style="list-style-type: none"> • Pediatric patients admitted to PICU who received VAN+TZP or VAN+CRO • Excluded <48 hrs treatment, AKI in first 24 hrs, underlying renal disease, RRT | VAN+TZ O VAN+CR O | Total 93 VAN+TZP: 58 V+CRO: 35 | (22) | AKI rate <ul style="list-style-type: none"> • VAN+TZ P: 25.9% • V+CRO: 8.6% • p = 0.041 • aOR 4.55 [1.11-18.7] |
|------------------------|---|--|----------------------------|--------------------------------------|------|---|

Footnote: (6) – vancomycin consensus guidelines AKI definitions; (19) – RIFLE guidelines AKI definitions; (20) – Acute kidney injury network AKI definitions; (21) – KDIGO AKI guidelines; (22) – modified RIFLE for pediatrics; aHR – adjusted Hazard ratio; AKI – acute kidney injury; ANC – absolute neutrophil count; aOR – adjusted Odds ratio; BUN – blood urea nitrogen; CF – cystic fibrosis; CFP – cefepime; CKD – chronic kidney disease; CrCl – creatinine clearance; CRO – ceftriaxone; ECMO – extracorporeal membrane oxygenation; ESRD – end-stage renal disease; HCT – hematopoietic cell transplant; KDOQI - Kidney Disease Outcomes Quality Initiative; KW – Kruskal-Wallis test; MEM – meropenem; N – number; OR – odds ratio; PICU – pediatric intensive care unit; PMH – past medical history; RRT – renal replacement therapy; SCr – serum creatinine; TZP – piperacillin/tazobactam; VAN – vancomycin; VTr – vancomycin trough level.

Chapter 2: Nephrotoxicity during Vancomycin Therapy in Combination with Piperacillin-Tazobactam or Cefepime

Rutter WC, Cox JN, Martin CA, Burgess DR, Burgess DS. Nephrotoxicity during Vancomycin Therapy in Combination with Piperacillin-Tazobactam or Cefepime. Antimicrobial Agents and Chemotherapy. 2016 Nov 28;AAC.02089-16.

Abstract

Background: Recent reports have demonstrated that vancomycin (VAN) may lead to an increase in acute kidney injury (AKI) when combined with anti-pseudomonal beta-lactams. This study compared the incidence of AKI associated with VAN plus piperacillin-tazobactam (TZP) or cefepime (CFP).

Methods: This was a retrospective, matched cohort study at an academic medical center between September 2010 and September 2014 including adult patients receiving VAN+TZP or VAN+CFP for at least 48 hours and without severe chronic or structural kidney disease, dialysis, pregnancy, cystic fibrosis, or hospital transfer. The primary outcome was difference in AKI incidence between VAN+TZP and VAN+CFP, evaluated using RIFLE criteria. Patients were matched based on: age, sex, severity of illness, baseline creatinine clearance, hypotension, number of nephrotoxicity risk factors, and IV contrast exposure.

Key Results: In total, 4,193 patients met all inclusion criteria (3,605 received VAN+TZP and 588 received VAN+CFP). The unadjusted AKI incidence was 21.4% in patients receiving VAN+TZP compared to 12.6% in VAN+CFP ($p < 0.001$). After matching, 1,633 patients receiving VAN+TZP and 578 patients receiving VAN+CFP were evaluated. The AKI incidence remained higher in patients receiving VAN+TZP compared to VAN+CFP (21.4% vs. 12.5%, $p < 0.0001$). This trend remained true for all classifications of the RIFLE criteria. After controlling for

remaining confounders, VAN+TZP therapy was associated with 2.18 times the odds of AKI compared to VAN+CFP (95% CI 1.64-2.94) in logistic regression.

Conclusions: AKI was significantly more common in patients receiving vancomycin in combination with piperacillin-tazobactam than cefepime. This finding reinforces the need for judicious use of combination empiric antimicrobial therapy.

Background

Nephrotoxicity is a well-established adverse effect of vancomycin therapy. Risk factors for increased acute kidney injury (AKI) with vancomycin include: administration with concomitant nephrotoxic agents, prolonged treatment durations greater than 7 days, daily vancomycin doses of 4 grams or greater, and obesity.(6) The incidence of AKI with vancomycin varies widely and is estimated to be 1.0 to 42%.(3–5) Additionally, current methicillin-resistant *Staphylococcus aureus* (MRSA) treatment guidelines advocate using more aggressive dosing to combat increasing minimum inhibitory concentrations (MICs) associated with treatment failure.(7)

The addition of an anti-pseudomonal beta-lactam agent, such as piperacillin/tazobactam (TZP) or cefepime (CFP), is common in hospitalized patients. Beta-lactam antibiotics, primarily penicillin agents and early first generation cephalosporins, have been associated with acute interstitial nephritis (AIN).(8) Cases of cefepime-associated AIN have only been reported recently.(9) Recent literature suggests that the combination of vancomycin (VAN) and TZP is more nephrotoxic than VAN monotherapy and VAN combined with CFP.(12,23,24) However, the impact of TZP and VAN therapy may not be consistent among all patient populations.(28) No clear mechanism for the increase in AKI incidence in combination therapy is known. The rate of AKI associated with VAN+TZP therapy in previous studies ranges from 9.5% to 34.8% in a variety of patient populations.(11–13,17,23,24,28,33,34)

The objective of this study was to evaluate the incidence of AKI between two commonly prescribed antibiotic regimens in hospitalized patients, piperacillin/tazobactam with vancomycin and cefepime with vancomycin.

Methods

Study Design and Setting

This was a single-center, retrospective matched cohort study of patients admitted to University of Kentucky HealthCare Medical Center (UKMC) between September 1, 2010 and September 1, 2014. This study was reviewed and approved by the UK Institutional Review Board.

Patients received either the combination of VAN+TZP or VAN+CFP. VAN was dosed according to institutional policy.⁽⁴³⁾ Pharmacokinetic levels were monitored by pharmacists and dosage adjustments were made as clinically appropriate.

Data source

Patient data were collected from the University of Kentucky Center for Clinical and Translational Science Enterprise Data Trust (EDT). The EDT contains clinical data from the inpatient population of UKMC from 2006 to present. Data stored in the EDT includes: demographics, financial classification (Medicare, Medicaid, private insurance), provider-level detail (service line), medical diagnosis (International Classification of Diseases 9 [ICD-9] codes), medical procedures (Current Procedural Terminology [CPT] codes), lab tests and results, medication administration details, visit details (age, length of stay, etc.), and vital signs.

Patient selection

Patients were included if they were 18 years of age or older, hospitalized at UKMC between September 1, 2010 and September 1, 2014, and received either of the studied combinations for a minimum of 48 hours with at least 48 hours of overlapping antibiotic therapy. Patients were excluded if they had a past history of chronic kidney disease (Stage 3 or higher, via ICD-9 code), structural kidney disease, required dialysis, experienced AKI prior to antibiotic administration, experienced AKI within 48 hours of therapy initiation or greater than 7 days after the last dose of antibiotics, or had underlying renal dysfunction at the time of antibiotic initiation

(defined as an initial creatinine clearance ≤ 30 mL/min). Patients were also excluded from the study if they were pregnant, were diagnosed with cystic fibrosis, or were transferred from another hospital. Patients were followed throughout their stay until time of discharge.

Data collection

Data collected for each patient included: demographic data, visit details (length of stay, admitting and primary diagnosis codes), severity of underlying illness as defined by the Charlson Comorbidity Index (CCI),(44) all serum creatinine levels drawn per visit, receipt of other nephrotoxic agents (listed in Table 1), and any receipt of intravenous contrast agents. The initial serum creatinine concentration was used as the patient's baseline. Hypotension was defined as a diagnosis of hypotension by ICD-9 coding, mean arterial pressure less than 60mmHg, or use of vasopressor or inotrope therapy to maintain adequate perfusion. Contrast exposure was defined as exposure to an imaging procedure in which contrast is indicated, via Healthcare Common Procedure Coding System (HCPCS) codes. Doses and dosing schedules of studied antibiotics and all vancomycin serum concentrations were obtained. Antibiotic days of therapy were defined as receipt of at least one dose of antibiotic per day.

Study Outcomes

The primary outcome was the difference in AKI incidence between VAN+TZP and VAN+CFP. Secondary outcomes were AKI incidence based on dosing schemes and duration of therapy, time to AKI from initiation of therapy, hospital length of stay, and mortality (defined as in-hospital mortality and transfer to a hospice facility).

Development of AKI was evaluated using Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria.(19) The RIFLE criteria consists of three severity classes (risk, injury, failure) and two outcomes classes (loss of kidney function, end stage kidney

disease). Risk was defined as a decrease in glomerular filtration rate (GFR) of at least 25%, injury was a decrease in GFR of at least 50%, and failure was defined as decrease in GFR of 75% or more. The outcomes classes require diagnosis based on duration of renal dysfunction and were not evaluated in this study. GFR was estimated with the adjusted Cockcroft-Gault equation.(45)

Patient Matching

Antibiotic indications were unknown and antibiotic choice was prescriber specific, therefore, propensity scores for each patient were estimated to control for potential bias. Patients in the VAN+TZP group were matched three-to-one with the VAN+CFP group using a nearest neighbor propensity score algorithm(46) without replacement and caliper of 0.2 based on the following factors: age, gender, CCI, hypotension exposure, risk factor group (defined by number of nephrotoxic exposures: 0, 1, 2, 3, and ≥ 4), baseline creatinine clearance, and receipt of IV contrast. Additionally, patients were matched exactly on gender, hypotension exposure, risk factor group and IV contrast administration.

Statistical Analysis

Characteristics between groups were described using basic descriptive statistics with continuous variables being compared by Student's t-test or Wilcoxon Rank-Sum test and categorical variables compared with Chi-Square test or Fisher's exact test, as appropriate. The average treatment effect was calculated by taking the average difference in incidence of AKI in 1,000 counterfactual simulations after fitting logistic regression models based on each treatment group to the opposite population.(47,48) Following propensity score matching, simple logistic regression was performed on all variables. In addition to remaining covariate imbalances in the matched cohort, the variables with significant associations with AKI in univariate regressions were incorporated into the multivariate logistic regression. All statistical analysis was completed with RStudio v0.98 running R v3.1.2 (R Foundation for Statistical Computing, Vienna,

Austria).(49,50) Model fit was assessed with the standardized Hosmer-Lemeshow test(51) and C-statistic. All tests were two-tailed and significance was defined at an alpha of 0.05.

Results

Records for 10,141 patients were screened. After exclusion criteria were applied (Figure 1), 4,193 patients were analyzed for all outcomes. Of 3,605 patients receiving VAN+TZP who were evaluated in the unmatched analysis, 1,633 patients were matched to 578 patients of 588 (>98% matched) in the VAN+CFP group. Of the 152 patients excluded due to an AKI occurring within 48 hours after treatment initiation, 133 were from the VAN+TZP group (3.6% of VAN+TZP population) and 19 were from the VAN+CFP group (3.1% of VAN+CFP population). This difference was not statistically significant ($p=0.68$), suggesting that the assumption that AKIs occurring prior to 48 hours of treatment are independent of drug selection.

At baseline, VAN+TZP group was older (51.5 ± 16.0 vs. 49.4 ± 17.0 years, $p=0.006$) and more likely to be male (60.4% vs. 55.4%, $p=0.03$). Severity of illness was similar between groups, while patients in the VAN+CFP group had higher baseline CrCl (101 [IQR 74-125] vs 97 [77-133] mL/min, $p=0.01$). Significant differences in nephrotoxic exposures existed between groups (Table 1). The median number of nephrotoxic risk factors in each group was 1 (IQR 0-2, $p=0.2$); however, VAN+CFP patients had more patients with ≥ 4 risk factors (7.8 vs. 3.8%, $p=0.0003$). Contrast exposure was more frequent in the VAN+CFP group (58.3 vs 45.3%, $p < 0.0001$). Among patients who had VAN concentrations obtained, no significant difference in VAN exposure was found. However, the VAN+CFP group had statistically higher average daily VAN doses. Antibiotic days of therapy were similar between groups; however, due to the large sample size and statistical power, the p-values are reported as significant.

AKI incidence was significantly higher in patients receiving VAN+TZP compared to patients receiving VAN+CFP (21.4% vs. 12.6%, $p < 0.0001$). Risk (11.7 vs 7.5%; $p = 0.003$) and

injury (6.8 vs. 4.6%; $p = 0.004$) classifications were more common in the VAN+TZP group. Failure classification was not significantly different between groups (Table 2).

Following matching, baseline covariates were well balanced with the remaining imbalances being present in acyclovir exposure, aminoglycoside exposure, and average daily VAN dose (Table 1). AKI remained more common in the VAN+TZP group (21.4% vs 12.5%, $p < 0.0001$) with all levels of the RIFLE criteria being more common in the VAN+TZP group (Table 2). VAN+CFP treatment was associated with an average treatment effect of 10.1% (95% CI; 7.8 to 12.2%) reduction in AKI incidence compared to VAN+TZP.

After controlling for additional confounders present after matching in the multivariate regression analysis (Table 3), VAN+TZP was associated with 2.18 times the odds of AKI when compared to VAN+CFP (95% CI, 1.64-2.94). Other independent risk factors for AKI included dehydration and exposure to acyclovir, amphotericin B, or loop diuretics. VAN doses between 3 and 4 g daily were associated with an increase in AKI (aOR 1.61; 95% CI 1.11-2.32) compared to those receiving between 1000 and 1500 mg per day. Duration of VAN treatment of at least 7 days was associated with 1.47 (95% CI 1.14-1.89) times the odds of AKI compared to those receiving VAN for less than 7 days. No evidence of overfitting was found (Hosmer-Lemeshow p -value = 0.53) and the model was adequately predictive with a c-statistic of 0.7.

Analyses of secondary objectives are summarized in Table 4. There were no significant differences in length of stay or mortality. AKI occurred earlier in VAN+TZP patients in both cohorts. The most common TZP dosing regimen in the VAN+TZP group was 3.375 g every 6 hours (55.6%) with 4.5 g every 6 hours being the second most common (30.4%). AKI incidence was significantly higher in patients receiving TZP 4.5g every 6 hours compared to patients receiving TZP 3.375g every 6 hours (24.3% vs. 20.1%, $p=0.008$), but was only significant for risk when stratified based on RIFLE. The most common CFP regimen was 2 g every 8 hours (64.8%)

with 2 g every 12 hours being the second most common (23.8%). There was no difference in AKI among patients receiving the highest CFP dosing regimen compared to all other regimens (13.4% vs. 11.1%; $p=0.5$).

Discussion

In this large retrospective review of patients receiving VAN-TZP or VAN-CFP, we found that the incidence of AKI was significantly higher in patients receiving VAN and TZP concomitantly. To our knowledge, this is the largest study to date that examines the difference in AKI incidence among patients treated with VAN and CFP or TZP. We found the AKI rate in patients treated with VAN-TZP to be 21.4% compared to the range of 9.5 to 34.8% found in the current literature.(11–13,17,23,24,28,33,34) The AKI incidence in the VAN-CFP group was similar to previous reports of 12.5%.(23,24) Of note, our findings in the VAN-CFP group were significantly lower than the Hammond, et al study (12.5 vs. 28.8%),(28) likely due to dissimilar patient populations.

In a 2014 review of 139 diabetic patients with osteomyelitis, VAN-TZP was associated with 29.3% incidence of acute renal failure (defined as an increase of 0.5 mg/dL in serum creatinine or 50% increase from baseline) compared to 13.3% in the VAN-CFP group ($p=0.099$).⁽²³⁾ Gomes and colleagues (2014) conducted a retrospective review of 224 patients receiving the combination of VAN and TZP or CFP.⁽²⁴⁾ In univariate analysis, VAN-TZP was associated with an AKI incidence of 34.8% compared to 12.5% for VAN-CFP ($p<0.0001$). Additionally, they found that TZP was an independent predictor of AKI in multiple logistic regression modelling. Finally, in a review of 122 critically ill patients, Hammond et al found no difference in AKI incidence among patients treated with VAN-TZP and VAN-CFP (32.7 vs 28.8%, respectively; $p=0.647$).⁽²⁸⁾

Small sample sizes and lack of statistical power severely limit the application of the previous studies. In addition, aside from the Gomes study, confounding was not adequately addressed, further limiting their application. Our study attempted to rectify these issues by including a larger number of patients (4,193 vs. 485 combined) and utilizing a propensity score matching algorithm to control for confounders. The difference in AKI incidence was maintained after controlling for confounders suggesting that the use of TZP is associated with increasing rates of AKI when compared to CFP when combined with VAN.

Vancomycin exposure was statistically different in both the unmatched and matched cohorts; however, the difference between median daily vancomycin doses is likely clinically irrelevant. To control for the statistical imbalance in doses greater than 4,000 mg per day, we included vancomycin dose in the multivariate regression analysis and found that vancomycin dose is largely uncorrelated with AKI incidence, with the exception of doses between 3,000 and 3,999 mg per day. Additionally, we found that vancomycin duration of therapy greater than 7 days was associated with higher rates of AKI, independent of treatment group. This may be related to the overall vancomycin exposure and warrants further study. However, when an interaction term between vancomycin dose and duration of therapy greater than 7 days was included in the multivariate logistic regression model, no significant interaction was found. Vancomycin troughs were analyzed, but no significant difference was found between groups and no association with AKI was found. This may be due to many patients not having trough values obtained; however, there were no significant differences in the number of troughs obtained between VAN+TZP or VAN+CFP in both unmatched and matched cohorts.

In our secondary outcomes, there was a numerically higher rate of in-hospital mortality among patients in the VAN+CFP group which did not reach statistical significance. This finding warrants further study; however, VAN+CFP patients had numerically higher rates of hypotension

which may indicate higher rates of acute illness not captured by surrogate variables and a predisposition to experience mortality.

We found several factors aside from treatment group that were independently associated with AKI incidence. This emphasizes that kidney injury is multifactorial. Additionally, use of other nephrotoxic agents may indicate underlying conditions not captured through our data analysis, such as use of loop diuretics in patients with uncontrolled heart failure, that may increase the risk of AKI independent of antibiotic selection.

This study has several limitations which must be addressed. Primarily, due to the retrospective nature of this analysis, demonstrating causality is difficult. However, several mechanisms to make the investigation more rigorous were applied, such as propensity score matching. In addition, rather than using parameter estimates from matched cohorts, counterfactual simulations were utilized to predict the average treatment effect on AKI incidence between groups. We employed a rigorous study design that controlled for major confounders of AKI, such as concomitant nephrotoxic exposure, hypotension, and previous renal disease. Nephrotoxic potential of agents was assumed to be equal, which is not necessarily true. Additionally, the binary representation of nephrotoxic exposure does not describe the amount of the agent received; as such, our estimations of AKI odds may be artificially elevated. Finally, data was collected retrospectively from the electronic medical record and is subject to inaccuracies documented in the chart; however, any bias introduced should be nondifferential.

In conclusion, in this large retrospective study, we found that AKI incidence among patients treated with a combination of piperacillin-tazobactam and vancomycin was significantly higher than in patients who were treated with cefepime and vancomycin. This finding remained after propensity score matching and after controlling for remaining imbalances in covariates. A mechanism for the increase in AKI among patients treated with piperacillin-tazobactam compared

to cefepime has not been proposed. Further animal and human studies are warranted to elucidate this mechanism.

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WCR and DSB had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Figures and tables

Table 2.1: Patient Demographic and Clinical Characteristics

| Variable | Unmatched Cohort Characteristics | | | Matched Cohort Characteristics | | |
|---|----------------------------------|--------------------|---------|--------------------------------|--------------------|---------|
| | VAN+TZP n = 3605 | VAN+CFP n = 588 | p value | VAN+TZP n = 1633 | VAN+CFP n = 578 | p value |
| Age (years) ^a | 51.5 ±16 | 49.4±17 | 0.006 | 49.7±15.7 | 49.4±17 | 0.7 |
| Male gender | 2177 (60.4) | 326 (55.4) | 0.03 | 905 (55.4) | 323 (55.9) | 0.9 |
| Charlson Comorbidity Index ^b | 3 (1-6) | 3 (1-5) | 0.2 | 3(1-5) | 3 (1-5) | 1 |
| Baseline Cl _{Cr} (mL/min) ^b | 97 (74 - 125) | 101 (77- 132) | 0.01 | 100 (77- 126) | 101 (77- 132) | 0.4 |
| Hypotension | 946 (26.2) | 190 (32.3) | 0.002 | 479 (29.3) | 186 (32.2) | 0.2 |
| Dehydration | 220 (6.1) | 36 (6.1) | 1 | 98 (6.0) | 34 (5.9) | 1 |
| Nephrotoxic Drug Exposure | 2190 (60.7) | 349 (59.4) | 0.5 | 939 (57.5) | 340 (58.8) | 0.6 |
| ACEI/ARB | 841 (23.3) | 139 (23.6) | 0.9 | 370 (22.7) | 135 (23.4) | 0.8 |
| Acyclovir | 70 (1.9) | 33 (5.6) | <0.0001 | 28 (1.7) | 29 (5.0) | <0.0001 |
| Aminoglycoside | 473 (13.1) | 101 (17.2) | 0.01 | 209 (12.8) | 98 (17.0) | 0.02 |
| Amphotericin B | 63 (1.7) | 16 (2.7) | 0.1 | 27 (1.7) | 15 (2.6) | 0.2 |
| Calcineurin Inhibitor | 114 (3.2) | 19 (3.2) | 1 | 35 (2.1) | 19 (3.3) | 0.2 |
| Contrast Dye | 1632 (45.3) | 343 (58.3) | <0.0001 | 921 (56.4) | 336 (58.1) | 0.5 |
| Foscarnet | 9 (0.2) | 1 (0.2) | 1 | 3 (0.2) | 1 (0.2) | 1 |
| Loop diuretic | 1121 (31.1) | 166 (28.2) | 0.2 | 496 (30.4) | 160 (27.7) | 0.2 |
| NSAID | 547 (15.2) | 88 (15.0) | 0.9 | 242 (14.8) | 83 (14.4) | 0.8 |
| Sulfonamide | 66 (1.8) | 9 (1.5) | 0.7 | 27 (1.7) | 9 (1.6) | 1 |
| Tenofovir | 21 (0.6) | 4 (0.7) | 0.8 | 8 (0.5) | 4 (0.7) | 0.5 |
| Number of risk factors | | | 0.0003 | | | 0.3 |
| 0 | 1132 (31.4) | 177 (30.1) | | 531 (32.5) | 177 (30.6) | |
| 1 | 1163 (32.3) | 190 (32.3) | | 528 (32.3) | 187 (32.4) | |
| 2 | 795 (22.1) | 113 (19.2) | | 335 (20.5) | 113 (19.6) | |
| 3 | 379 (10.5) | 62 (10.5) | | 160 (10.4) | 60 (10.4) | |
| ≥4 | 136 (3.8) | 46 (7.8) | | 79 (7.1) | 41 (7.1) | |
| Daily VAN dose (mg/day) ^b | 2000 (1500-2500) | 2083 (1600-2737) | <0.0001 | 2000 (1500-2500) | 2083 (1600-2700) | 0.002 |
| Daily VAN dose ≥4000mg | 39 (1.1) | 16 (2.7) | 0.002 | 18 (1.1) | 16 (2.8) | 0.009 |

Table 2.1 (continued)

| | | | | | | |
|---|------------|------------|---------|------------|-----------|---------|
| Max VTr | | | 0.3 | | | 0.7 |
| <10mcg/mL | 438 (20.8) | 77 (21.1) | | 213 (21.8) | 76 (21.1) | |
| 10-15mcg/mL | 507 (24.1) | 100 (27.4) | | 231 (23.7) | 98 (27.2) | |
| 15-20mcg/mL | 521 (24.8) | 88 (24.1) | | 239 (24.9) | 87 (24.2) | |
| >20mcg/mL | 639 (30.4) | 100 (27.4) | | 293 (30.0) | 99 (27.5) | |
| Total Antibiotic Days of Therapy ^b | 5 (4-8) | 5 (4-8) | 0.05 | 5 (4-8) | 5 (4-8) | 0.4 |
| Combination Therapy | 3 (3-5) | 4 (3-6) | 0.001 | 4 (3-5) | 4 (3-6) | 0.008 |
| CFP or TZP Therapy | 5 (3-7) | 5 (3-7) | 0.8 | 5 (3-7) | 5 (3-7) | 0.2 |
| VAN Therapy | 4 (3-6) | 4 (3-7) | <0.0001 | 4 (3-6) | 4 (3-7) | <0.0001 |

Footnote for Table 2.1:

Data are number (percentage) unless otherwise indicated; ^aMean ± standard deviation; ^bMedian (IQR). ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ClCr = creatinine clearance; CFP = cefepime; NSAID = non-steroidal anti-inflammatory drug; TZP = piperacillin-tazobactam; VAN = vancomycin; VTr = VAN trough.

Table 2.2: Incidence of AKI in unmatched and matched cohorts

| Outcome | Unmatched Cohort | | | Matched Cohort | | |
|---------|--------------------|------------------|---------|--------------------|------------------|---------|
| | VAN-TZP N=3,605 | VAN-CFP N=588 | p-value | VAN-TZP N=1,633 | VAN-CFP N=578 | p-value |
| Any AKI | 771 (21.4%) | 74 (12.6%) | <0.0001 | 349 (21.4%) | 72 (12.5%) | <0.0001 |
| Risk | 422 (11.7%) | 44 (7.5%) | 0.003 | 179 (11.0%) | 42 (7.3%) | 0.01 |
| Injury | 244 (6.8%) | 21 (3.6%) | 0.004 | 113 (6.9%) | 21 (3.6%) | 0.006 |
| Failure | 105 (2.9%) | 9 (1.5%) | 0.08 | 57 (3.5%) | 9 (1.6%) | 0.03 |

Footnote for Table 2.2:

Data are number (percentage); CFP = cefepime; TZP = piperacillin-tazobactam; VAN = vancomycin.

Table 2.3: Multivariate regression results in matched cohort

| Covariate | Odds Ratio | Confidence Interval | p value |
|----------------------------------|------------|---------------------|---------|
| Treatment Group | | | |
| VAN+TZP | | <i>(reference)</i> | |
| VAN+CFP | 2.18 | 1.64-2.94 | <0.001 |
| VAN Dose (mg/day) | | | |
| <1000mg | 0.53 | 0.16-1.39 | 0.3 |
| 1000-1499mg | 1.01 | 0.72-1.42 | 0.9 |
| 1500-1999mg | | <i>(reference)</i> | |
| 2000-2499mg | 1.08 | 0.79-1.48 | 0.6 |
| 2500-2999mg | 1.16 | 0.81-1.65 | 0.4 |
| 3000-3999mg | 1.61 | 1.11-2.32 | 0.01 |
| ≥4000mg | 1.3 | 0.5-3.05 | 0.6 |
| VAN Duration of Therapy ≥ 7 days | 1.47 | 1.14-1.89 | 0.003 |
| Acyclovir Exposure | 2.22 | 1.17-4.07 | 0.01 |
| Amphotericin B Exposure | 2.25 | 1.14-4.41 | 0.02 |
| Loop Diuretic Exposure | 2.78 | 2.22-3.50 | <0.001 |
| Calcineurin Inhibitor Exposure | 1.62 | 0.85-2.98 | 0.1 |
| Dehydration Exposure | 1.81 | 1.18-2.72 | 0.005 |

Footnote for Table 2.3:

CFP = cefepime; TZP = piperacillin-tazobactam; VAN = vancomycin.

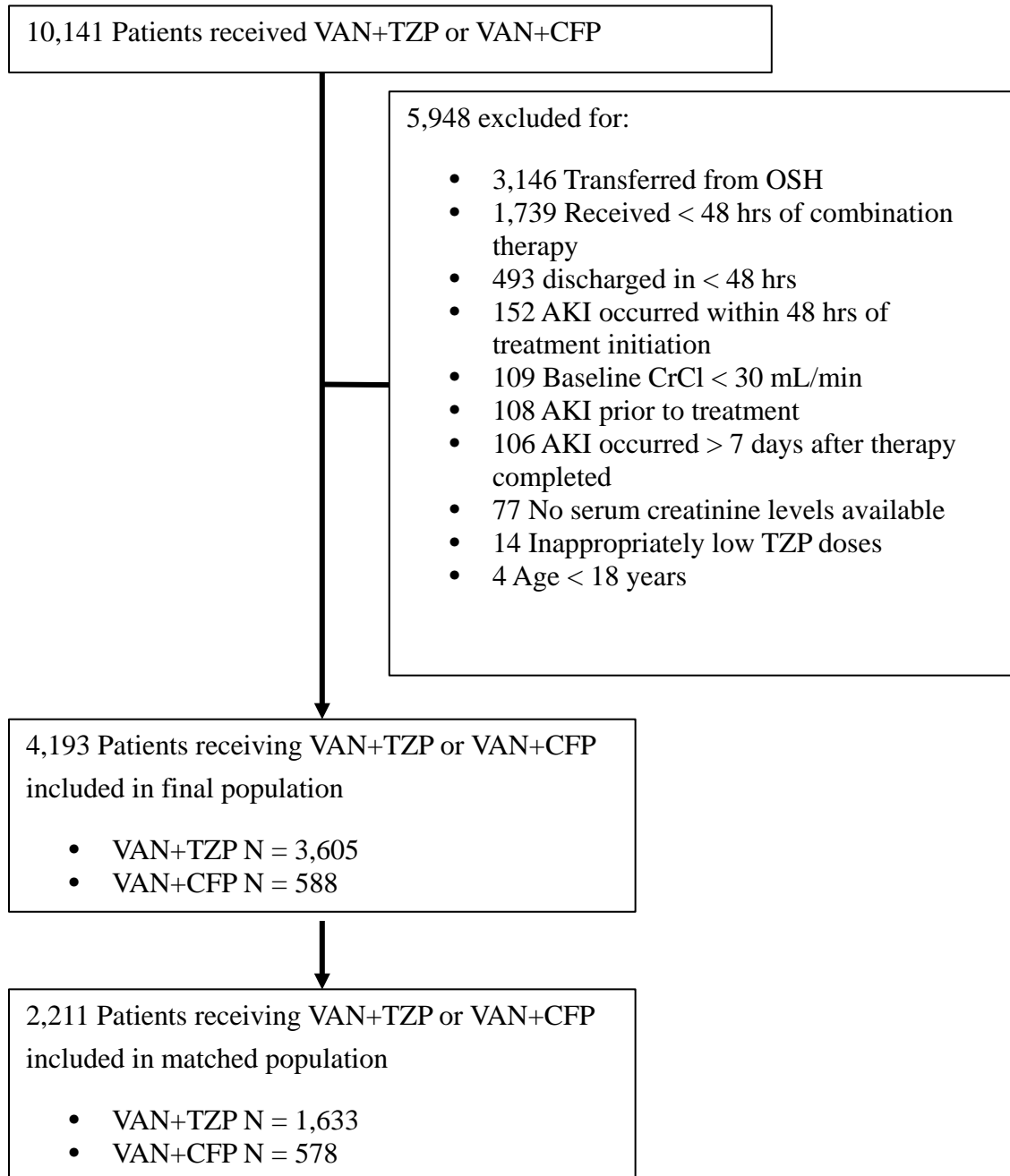
Table 2.4: Secondary endpoints

| Characteristic | Unmatched Cohort | | | Matched Cohort | | |
|--------------------------------------|--------------------|------------------|---------|--------------------|------------------|---------|
| | VAN-TZP N=3,605 | VAN-CFP N=588 | p-value | VAN-TZP N=1,633 | VAN-CFP N=578 | p-value |
| Time to AKI ^a | 5 (3-9) | 8 (4-16.8) | 0.0006 | 5 (3-9) | 8 (4-17) | 0.0004 |
| Hospital Length of Stay ^a | 8 (4-15) | 8 (4-17) | 0.08 | 8 (4-15) | 8 (5-17) | 0.9 |
| In-hospital Mortality | 276 (7.7%) | 53 (9.0%) | 0.3 | 113 (6.9%) | 53 (9.2%) | 0.09 |

Footnote for Table 2.4:

Data are number (percentage) unless otherwise indicated; ^aMedian (IQR). CFP = cefepime; TZP = piperacillin-tazobactam; VAN = vancomycin.

Figure 2.1: Patient selection diagram



Footnote for Figure 2.1:

CrCl=creatinine clearance; CFP = cefepime; OSH = outside hospital; TZP = piperacillin-tazobactam; VAN = vancomycin.

Chapter 3: Incidence of Acute Kidney Injury Among Patients Treated with Piperacillin-Tazobactam or Meropenem in combination with Vancomycin

Rutter WC, Burgess DS. Incidence of Acute Kidney Injury Among Patients Treated with Piperacillin-Tazobactam or Meropenem in combination with Vancomycin. Antimicrobial Agents and Chemotherapy (under review)

Abstract

Acute kidney injury increases during empiric antimicrobial therapy with the combination of piperacillin-tazobactam (TZP) and vancomycin (VAN) when compared to monotherapy or the combination of cefepime and VAN. Limited data regarding the impact of meropenem (MEM) combined with VAN exist. This study examined the AKI incidence among patients treated with MEM+VAN or TZP+VAN. Data were collected from the University of Kentucky Center for Clinical and Translational Science Enterprise Data Trust from September 2007 through October 2015. Adults without previous renal disease, who received MEM+VAN or TZP+VAN for at least 2 days were included. Inverse probability of treatment weighting was utilized to control for differences between groups. In total, 10,236 patients met inclusion criteria, with 9,898 receiving TZP+VAN and 338 receiving MEM+VAN. AKI occurred in 15.4% of MEM+VAN patients compared to 27.4% of TZP+VAN patients ($p < 0.001$). TZP+VAN was associated with increased AKI compared to MEM+VAN (OR=2.53; 95% CI 1.82-3.52), after controlling for confounders. MEM+VAN should be considered an appropriate alternative therapy to TZP+VAN if nephrotoxicity is a major concern. The results of this study demonstrate that judicious use of TZP+VAN for empiric coverage of infection is needed.

Background

Empiric combination antimicrobial therapy is critical for the treatment of infections and sepsis.(54,55) Piperacillin-tazobactam (TZP) is a beta-lactam/beta-lactamase inhibitor combination that is frequently used concomitantly with vancomycin (VAN) for empiric coverage of infections. This combination provides coverage of clinically important gram-negative and gram-positive organisms. While generally considered safe, recent literature suggests a significant increase in the incidence of nephrotoxicity with the TZP+VAN combination when compared to either agent as monotherapy or to other empiric combination.(11,12,18,24,56,57) However, this phenomenon has not been noted in all studies.(23,28)

While studies have demonstrated that TZP+VAN has significantly increase AKI incidence compared to cefepime and VAN,(24,27,57) only one study to date has attempted to compare TZP+VAN to meropenem (MEM) and VAN.(58) In this study, Al Yami was unable to find a significant difference in AKI incidence among patients receiving TZP+VAN compared to MEM+VAN. However, this is limited by small sample size and lower than anticipated overall AKI incidence.

The current study was designed to determine if a difference in AKI incidence exists between TZP or MEM when combined with VAN, with the hypothesis that TZP+VAN would exhibit increased AKI incidence compared to MEM+VAN.

Methods

This was an IRB-approved, retrospective cohort study of adult patients admitted to the University of Kentucky Medical Center (UKMC) between September 2007 and October 2015. Patients were included if they received MEM or TZP in combination with VAN for at least 2 days. Patients with a past medical history of cystic fibrosis, chronic kidney disease, or hemodialysis were excluded. Additionally, pregnant or breastfeeding patients were excluded.

Data were obtained from the University of Kentucky Center for Clinical and Translational Science Enterprise Data Trust (EDT). The EDT is an electronic repository of clinical data collected at UKMC and contains a copy of the digital health record. The EDT is updated nightly and contains: demographics, financial classification, provider-level detail, medical diagnosis, medical procedures, lab tests and results, medication administration details, visit details, and vital signs. Data collected included: patient demographics and visit information, antimicrobial drug administration data, concomitant nephrotoxin administration, laboratory results, and baseline comorbidity information.

The primary outcome of this study was the incidence of AKI as defined by the glomerular filtration rate (GFR) criteria of Risk, Injury, Failure, Loss, and End-stage (RIFLE) criteria.⁽¹⁹⁾ GFR was estimated with the adjusted Cockcroft-Gault equation⁽⁴⁵⁾ at baseline and throughout each patient's hospitalization. AKI that occurred before treatment, within 48 hours treatment initiation, or after 7 days after treatment discontinuation were excluded. Secondary outcomes included length of hospitalization and inpatient mortality, defined as mortality on date of discharge or transfer to hospice.

Severity of baseline comorbidity was assessed with the Charlson comorbidity index (CCI).⁽⁴⁴⁾ Hypotension was defined as mean arterial pressure < 65 mmHg or exposure to vasopressors. Concomitant nephrotoxin exposure was assessed as receiving at least one dose of the agent within 24 hours of initiation of TZP or MEM through the duration of therapy. Concomitant nephrotoxins analyzed included: aminoglycosides, amphotericin B, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, IV radiocontrast dye, loop diuretics, non-steroidal anti-inflammatory drugs, calcineurin inhibitors, and vasopressors.

Basic descriptive statistics were performed. Continuous variables were assessed with the Student's *t* test or Wilcoxon test as appropriate. Categorical variables were assessed with a chi-

square or Fisher's exact test. Following bivariable analysis, variables that significantly differed between groups were included in an inverse probability of treatment model to generate weights for the final logistic regression model of AKI odds.(59) Statistical significance was defined as alpha 0.05. All data analysis and statistical procedures were conducted with R v3.3.2 (Vienna, Austria) and RStudio v0.99.903 (Boston, MA). (49,50)

Results

In total, 10,236 patients met all inclusion criteria, with 338 receiving MEM+VAN and 9,898 receiving TZP+VAN. Mean age was 53.7 (\pm 16.4) years of age and 58.8% of patients were males (Table 1). At baseline the MEM+VAN cohort tended to be more ill than those in the TZP+VAN cohort (CCI 4 [2-6] vs 3 [1-7], $p=0.014$) and more MEM+VAN patients had baseline CrCl \geq 90 mL/min (58.5% vs 50.6%, $p = 0.011$). Significantly more patients had diabetes mellitus (34.0% vs. 28.0%, $p=0.018$) and hypotension (60.9% vs. 51.8%, $p = 0.001$) in the MEM+VAN group with a trend toward significance in heart failure. The MEM+VAN cohort were more likely to be exposed to concomitant aminoglycosides (3.5% vs. 1.5%, $p = 0.007$), calcineurin inhibitors (6.5% vs. 3.7%, $p = 0.011$), and vasopressors (16.3% vs. 11.3%, $p = 0.006$).

AKI occurred in 2,765 (27.0%) patients overall, with AKI being more common in the TZP+VAN group (27.4% vs. 15.4%, $p<0.0001$). Risk and injury stratifications were significantly more common among the TZP+VAN cohort (15.3% vs. 9.8%, $p = 0.006$, and 7.8% vs. 3.5%, $p = 0.005$, respectively; Figure 1). There was no significant difference in failure stratification (4.2% vs. 2.1%, $p = 0.068$).

In inverse probability weighted logistic regression, TZP+VAN treatment was associated with a significant increase AKI odds compared with MEM+VAN (odds ratio = 2.53; 95% confidence interval 1.82 – 3.52).

Secondary endpoints did not differ between treatment group with 10.3% and 11.6% of patients in the MEM+VAN and TZP+VAN group experiencing mortality, respectively. Median length of stay was similar between cohorts (MEM+VAN 9 [6-15] vs. TZP+VAN 10 [5-18] days, $p=0.482$).

Discussion

In this large retrospective study of AKI among patients receiving meropenem or piperacillin-tazobactam in combination with vancomycin, we found that combination therapy with piperacillin-tazobactam is associated with significant increases in AKI incidence when compared to meropenem combination therapy. To our knowledge, this is the largest study to examine this comparison.

Previous investigations of AKI related to TZP+VAN therapy have shown incidence ranges from 9.5% to 34.8%.^(24,33) Our findings are consistent with this estimate with 27.4% of TZP+VAN patients experiencing an AKI during therapy. The rate of MEM+VAN-related AKI in the present study differ significantly from the study by Al Yami (15.4% vs. 5.33%).⁽⁵⁸⁾ This may be due to differences in patient populations or AKI definitions. It is important to note that our study included a heterogeneous population of critically ill and general medicine patients. Additionally, patients in the TZP+VAN cohort in the Al Yami study had lower AKI incidence compared to previous literature (7.41%). Our study differs by having a larger patient sample (10,236 vs. 183) than the previous study on this topic, ensuring statistical power to detect a difference in AKI incidence and control for confounding.

The current study has several limitations. This was a retrospective study, which limits the causal relationship between drug exposure and outcome; however, we established a temporal link and restriction that links the incidence of AKI with administration of the medications being studied. Additionally, to mimic randomization and limit the impact of confounders, we performed

inverse probability weighting to create a balanced pseudo-population on which the regression analysis was performed. Sensitivity analyses suggest that the inverse probability scores were adequate. Nephrotoxin exposures were assessed as binary variables, which does not account for any dosing frequency or intensity. This may change the estimate of the confounding variables; however, sensitivity analyses using nephrotoxin days of therapy, suggests that the binary treatment is acceptable. Further work to identify optimal handling of concomitant nephrotoxins is needed. Duration of beta-lactam infusion was not assessed in this study; however, previous studies demonstrate that AKI incidence is not associated with duration of infusion.(33,34,60) Despite the rigorous study design, there is a possibility of uncontrolled confounding, as unknown confounders may remain.

In conclusion, we found a significant increase in AKI with TZP+VAN treatment compared to MEM+VAN treatment. This finding further underscores the need for judicious use of TZP+VAN as empiric antimicrobial therapy. Meropenem may be an acceptable alternative to piperacillin-tazobactam when nephrotoxicity is a major concern. Further studies of alternative combination therapies are needed to determine what alternatives have the best safety profile.

Acknowledgements

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Tables and Figures

Table 3.1: Patient characteristics

| Variable | Cohort n = 10,236 | VAN+MEM n = 338 | VAN+TZP n = 9,898 | p value |
|--|----------------------|----------------------|----------------------|---------|
| Age (mean[SD]) | 53.7 (16.4) | 52.3 (16.7) | 53.8 (16.4) | 0.122 |
| Gender | | | | 0.003 |
| Male | 6019 (58.8) | 172 (50.9) | 5847 (59.1) | |
| Female | 4217 (41.2) | 166 (49.1) | 4051 (40.9) | |
| Caucasian | 9201 (89.9) | 317 (93.8) | 8884 (89.8) | 0.020 |
| Weight (mean[SD]) | 83.3 (24.5) | 84.1 (24.7) | 83.3 (24.5) | 0.591 |
| BMI (mean[SD]) | 28.6 (16.8) | 29 (8.3) | 28.6 (17.0) | 0.431 |
| Charlson comorbidity index (median [IQR]) | 3 (1-7) | 4 (2-6) | 3 (1-7) | 0.014 |
| Baseline CrCl (median [IQR]) | 90.8 (65.6-120.7) | 98.3 (69.7-132.5) | 90.6 (65.5-120.4) | 0.002 |
| Baseline CrCl group | | | | 0.011 |
| 30-59 mL/min | 2015 (19.7) | 61 (18.0) | 1954 (19.7) | |
| 60-89 mL/min | 3018 (29.5) | 79 (23.4) | 2939 (29.7) | |
| ≥90 mL/min | 5203 (50.8) | 198 (58.5) | 5005 (50.6) | |
| Comorbidities | | | | |
| Diabetes mellitus | 2886 (28.2) | 115 (34.0) | 2771 (28.0) | 0.018 |
| Heart failure | 1549 (15.1) | 64 (18.9) | 1485 (15.0) | 0.057 |
| Hypertension | 5530 (54.0) | 192 (56.8) | 5338 (53.9) | 0.324 |
| Hypotension | 5337 (52.1) | 206 (60.9) | 5131 (51.8) | 0.001 |

Table 3.1 (continued)

| Concomitant nephrotoxins | | | | |
|--------------------------|--------------|------------|-------------|--------|
| Aminoglycoside | 1685 (16.5) | 60 (17.7) | 1625 (16.4) | 0.565 |
| Amphotericin B | 163 (1.6) | 12 (3.5) | 151 (1.5) | 0.007 |
| ACE inhibitor | 2029 (19.8) | 63 (18.6) | 1966 (19.9) | 0.627 |
| ARB | 303 (3.0) | 9 (2.7) | 294 (3.0) | 0.869 |
| Contrast dye | 522 (5.1) | 38 (11.2) | 484 (4.9) | <0.001 |
| Loop diuretic | 3708 (36.2) | 105 (31.1) | 3603 (36.4) | 0.051 |
| NSAID | 1558 (15.2) | 43 (12.7) | 1515 (15.3) | 0.221 |
| Calcineurin inhibitor | 386 (3.8) | 22 (6.5) | 364 (3.7) | 0.011 |
| Vasopressor | 1172 (11.4) | 55 (16.3) | 1117 (11.3) | 0.006 |

Figure 3.1: AKI rates among patients treated with piperacillin-tazobactam or meropenem in combination with vancomycin, stratified by RIFLE criteria

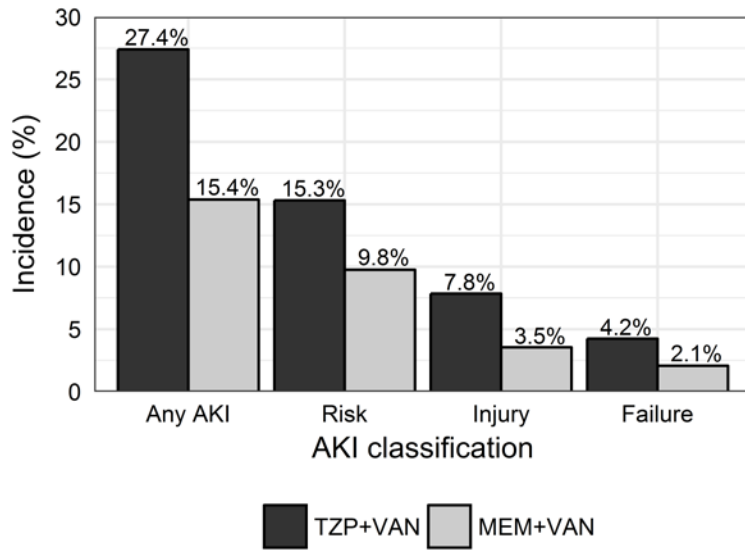
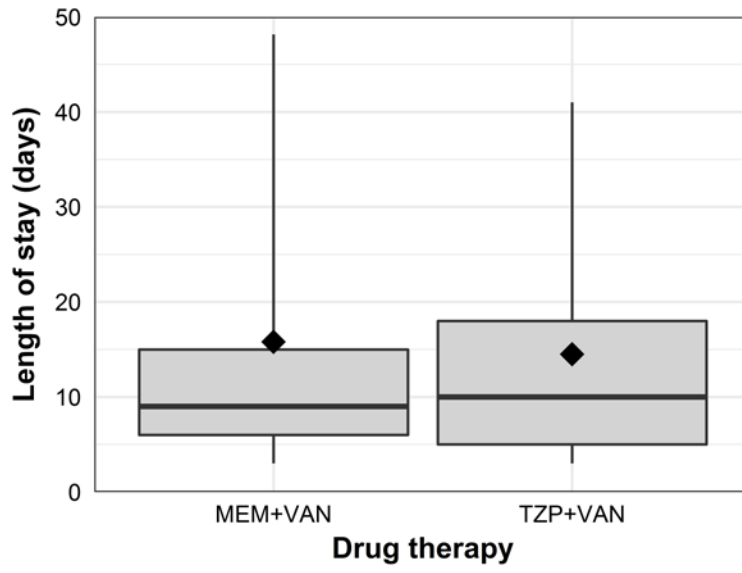


Figure 3.2: Length of stay between VAN+MEM and VAN+TZP cohorts



Chapter 4: Acute kidney injury in patients treated with IV beta-lactam/beta-lactamase inhibitor combinations

Rutter WC, Burgess DS. Acute Kidney Injury in Patients Treated with IV Beta-Lactam/Beta-Lactamase Inhibitor Combinations. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2017 May;37(5):593–8.

Abstract

Study Objective

Increased acute kidney injury incidence has been reported in patients receiving piperacillin-tazobactam (TZP) therapy compared to other beta-lactams. This study sought to determine if the addition of beta-lactamase inhibitors impact AKI incidence by comparing patients treated with TZP or ampicillin-sulbactam (SAM).

Design

Retrospective cohort study

Setting

Large academic tertiary care hospital

Patients

Overall, 2,448 patients received TZP (N=1,836) or SAM (N=612) for at least 48 hours between 9/1/2007 and 9/30/2015. Patients were excluded for: pregnancy, cystic fibrosis, chronic kidney disease, and initial creatinine clearance (CrCl) < 30 mL/min. Patients were matched on: Charlson Comorbidity Index (CCI), initial CrCl, hypotension exposure, various nephrotoxic drug exposures, history of diabetes, heart failure, and hypertension.

Measurements and Main results

AKI occurred in 265 patients and was similar among both groups (TZP 11.4% vs SAM 9.2%; $p=0.14$). After stratification by vancomycin exposure, and controlling for confounders, there was no difference in AKI odds between SAM and TZP (adjusted OR 0.87, 95% CI 0.59-1.25). The addition of vancomycin to TZP increased odds of AKI compared to TZP alone (adjusted OR 1.77, 95% CI 1.26-2.46). Concomitant SAM and VAN therapy was not associated with a significant increase in AKI compared to SAM monotherapy (adjusted OR 1.01, 95% CI 0.48-1.97).

Conclusion

AKI rates were similar between TZP and SAM in a matched cohort. The addition of a beta-lactamase inhibitor is not likely the mechanism in the observed increased rates of AKI in patients treated with vancomycin and TZP.

Background

Piperacillin-tazobactam in combination with vancomycin has been associated with elevated rates of AKI in many small retrospective studies. The AKI incidence ranges from 9.5 to 34.8%, depending on the target population.(12,13,17,23,24,28,33,34) The most common comparator agent has been cefepime(23,24,28), as piperacillin-tazobactam and cefepime share a similar niche in antipseudomonal therapy. In these comparisons, piperacillin-tazobactam is associated with higher rates of AKI. The mechanism for the increased AKI incidence observed is unknown; however, piperacillin-tazobactam is unique in that it contains a beta-lactam and a beta-lactamase inhibitor, which is similar in structure to other beta-lactams.

The primary objective of this study was to determine if there is a significant difference in AKI rate among patients who are treated with piperacillin-tazobactam or ampicillin-sulbactam. We hypothesize that these groups will have similar rates of AKI and therefore that the observed increase in AKI with piperacillin-tazobactam is not related to coadministration of a beta-lactam and beta-lactamase inhibitor.

Methods

This was an IRB-approved retrospective cohort study at the University of Kentucky HealthCare between 9/1/2007 and 9/30/2015. Adult patients receiving piperacillin-tazobactam (TZP) or ampicillin-sulbactam (SAM) for a least 48 hours were included. Patients were excluded if they were pregnant, had a past medical history of cystic fibrosis or chronic kidney disease, and if their initial creatinine clearance (CrCl) was less than 30 mL/min. Additionally, patients receiving other beta-lactam agents were excluded. To account for the impact of vancomycin on AKI, a subanalysis stratified by vancomycin exposure was conducted.

The primary outcome of this study was incidence of AKI, as defined by the RIFLE criteria.(19) Creatinine clearance was utilized as a marker for GFR and was estimated by the

adjusted Cockcroft-Gault equation.(45) Exposure to other nephrotoxic agents was defined as receipt of at least one dose within 24 hours of treatment initiation through treatment discontinuation. Nephrotoxic agents included in this analysis were: aminoglycosides, amphotericin B, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, intravenous radiocontrast dye, loop diuretics, non-steroidal antiinflammatory drugs, calcineurin inhibitors, vancomycin, and vasopressors. Hypotension was a composite of mean arterial pressure less than 65 mmHg, systolic blood pressure less than 90 mmHg, or vasopressor exposure during treatment. Charlson comorbidity index (CCI) was used to approximate underlying severity of chronic illness.(44)

Data was collected from the University of Kentucky Center for Clinical and Translational Science Enterprise Data Trust (EDT) and included demographic data, drug dosing and administration data, laboratory data, and comorbidity data. The EDT contains electronic medical record data from University of Kentucky HealthCare from 2006 to present. Data stored in the EDT includes: patient demographics, financial classification (Medicare, Medicaid, private insurance), provider-level details, diagnoses, procedures, lab tests and results, medication administration, visit details (age, length of stay, etc.), and vital signs. Patients were followed from admission to discharge.

Descriptive statistics were performed. Comparisons of continuous variables were completed with Student's t test or the Wilcoxon's rank-sum test. Categorical variables were compared with chi-squared or Fisher's exact tests as appropriate. Patients in the TZP and SAM groups were propensity score matched(46) based on: CCI; initial CrCl (30-59, 60-89, and >90 mL/min); hypotension exposure, exposure to aminoglycosides, amphotericin B, ACE inhibitors, loop diuretics, calcineurin inhibitors, or vancomycin; history of diabetes, heart failure, and hypertension, in a 3 to 1 fashion between TZP and SAM groups. These variables were selected

based on unadjusted associations with AKI in bivariate analysis and were equally weighted in the final propensity score model. Variables were analyzed in bivariate logistic regression with AKI as the response variable and all variables that were significant in simple regressions were included in the initial multivariate logistic regression of AKI. Variables were removed from the multivariate model in a step-wise fashion to minimize the Akaike Information Criterion for the final multivariate model presented. Additionally, goodness-of-fit was tested with the Hosmer-Lemeshow test and the area under the receiver-operator-characteristic curve (ROC) or c-statistic. All tests were two-tailed with an alpha of 0.05 consider significant. All data analyses were performed with R v3.1.3 and RStudio v0.98.(49,50)

Results

Following matching, 2,448 patients were analyzed for the primary outcome, with 1,836 patients receiving TZP and 612 receiving SAM. Baseline covariates (Table 1) were evenly distributed between both groups, with the exceptions of CCI (5 [IQR 2-9] vs. 4 [IQR 1-9] in SAM and TZP groups, respectively; $p=0.002$) and IV radiocontrast dye exposure (3.3% vs. 5.8% in SAM and TZP groups, respectively; $p=0.02$). Overall AKI incidence was similar between SAM (9.2%) and TZP (11.4%, $p=0.15$); however, TZP patients experienced higher rates of GFR decreases of greater than 50% (1.5% vs. 1.1%, $p=0.02$) and greater than 75% (1.3% vs. 0.2%, $p=0.0001$) (Table 2).

Vancomycin exposure was significantly associated with AKI independent of treatment group on bivariate logistic regression (OR 1.07; 95% CI 1.04-1.1). Table 3 shows the results of the subanalysis between groups stratified by vancomycin exposure. AKI incidence was lowest in the SAM group (8.9%) and highest in the TZP plus vancomycin group (18.1%). TZP alone was associated with a 9.5% AKI rate and SAM plus vancomycin had a 10.2% AKI rate. These stratified groupings were used in the multivariate regression model (Table 4). There was no

observed difference in odds of AKI between SAM and TZP (aOR 0.87, 95% CI 0.59-1.25); however, the addition of vancomycin to TZP significantly increases the odds of AKI compared to TZP monotherapy (aOR 1.77, 95% CI 1.26-2.46). This was not seen with concomitant VAN and SAM therapy compared to SAM monotherapy (aOR 1.01; 95% CI 0.48-1.97).

Additional factors that were independently predictive of AKI included duration of beta-lactam therapy, history of heart failure diagnosis, loop diuretic exposure and calcineurin inhibitor exposure (Table 4). There is no evidence of overfitting in the model with a Hosmer-Lemeshow p value of 0.37 and the model had an AUC under the ROC of 0.71.

Discussion

In this large retrospective cohort study, the AKI incidence between two common beta-lactam/beta-lactamase inhibitor combinations was found to be similar after controlling for confounding factors associated with AKI. To our knowledge, this is the first study to examine this relationship.

Previous literature in this area has shown high variability in the rates of AKI associated with TZP, mainly as combination therapy with vancomycin. Kim and colleagues reported TZP monotherapy-associated AKI to be approximately 15.4%, which was not significantly different from the combination therapy arm.(17) AKI rates when TZP is combined with VAN range from 9.5 to 34.8%.(12,13,17,23,24,28,33,34) Few studies have compared AKI incidence among different treatment regimens, but the most common comparator is cefepime due to the similar niche in therapy. Gomes and colleagues found TZP combined with VAN had significantly higher rates of AKI compared to the combination of cefepime and VAN (34.8% vs 12.5%).(24) In a study of diabetic osteomyelitis patients, although not statistically significant, TZP-VAN was associated with an AKI rate of 29.3% compared to 13.3% for cefepime-VAN.(23) Additionally, in critically ill patients, no difference in AKI incidence was noted between TZP or CFP when

combined with VAN.(28) These studies used varying definitions of AKI and examined relatively small sample sizes. Additionally, although cefepime and TZP are commonly interchanged clinically, TZP is distinct due to the addition of a beta-lactamase inhibitor to the beta-lactam. The unadjusted AKI rate in our study among patients in the TZP arm was 22.2%; however, following matching the AKI rate was only 11.4% in the TZP group (p=0.15). After stratification by vancomycin use, TZP-VAN was shown to have higher rates of AKI compared to TZP alone (18.1% vs. 9.5%; aOR 1.77; 95%CI 1.26-2.46), which is consistent with prior literature.

Ampicillin-sulbactam is another beta-lactam/beta-lactamase inhibitor combination used intravenously for the treatment of a variety of infections. Nephrotoxicity data for SAM are limited; however, one small study of high dose SAM for multidrug resistant *Acinetobacter baumannii* pneumonia found AKI rates of approximately 15.3%.(52) Another study, examining SAM use in multidrug resistant *Acinetobacter baumannii* infections found AKI renal failure occurred in 26% of patients.(53) These findings are limited by sample size and selection of critically ill patients, who have higher rates of nephrotoxicity. In contrast, we found that AKI occurred in 9.2% of patients receiving SAM. Distinct data for patients receiving SAM in combination with vancomycin is not readily available from the previous SAM studies. When stratified by vancomycin exposure, we found a numerical, but statistically insignificant increase in AKI (10.2% SAM-VAN vs 8.9% SAM alone; aOR 1.01, 95% CI 0.48-1.97).

Despite the marked interest in the increase in nephrotoxicity noted with combination TZP and VAN therapy, there have been no hypothesized pathophysiological mechanisms for this finding. We considered the addition of tazobactam to piperacillin as a possible contributing factor to the increase in AKI due to the administration of two beta-lactam-like agents. This is specifically important when comparing TZP-VAN to other beta-lactam combinations that only contain a single beta-lactam agent, such as cefepime or meropenem. Nephrotoxicity data for beta-

lactamase inhibitors administered alone are lacking. Ampicillin-sulbactam is the only beta-lactam/beta-lactamase inhibitor agent commonly used as an alternative to TZP at our institution. This study shows that AKI rates are similar among beta-lactam/beta-lactamase inhibitor combinations at our institution and that the combination of vancomycin and piperacillin-tazobactam is a major factor in AKI.

This study is not without limitations. While we employed a robust analysis via matching patients on several possible confounders, there is still the possibility of unmeasured confounders being present in our sample. However, we did control for many nephrotoxic exposures, such as hypotension and other nephrotoxic drug administration, which should explain the majority of confounding in this study. Additionally, we attempted to control for the temporal relation of nephrotoxic exposure to the treatment window of the study agents. For other nephrotoxic agents, dose-response relationships were not assessed and all exposures were defined as receipt of at least one dose within 24 hours prior to initiation of study agents. This may overestimate the impact of those exposures on AKI, which in turn would bias our results towards the null hypothesis. Differences in chronic illness, via CCI, between groups could bias results toward SAM being more nephrotoxic than TZP; however, our results state the opposite. Critical illness is not well captured by the CCI and there remains a chance that there is a higher proportion of critically ill patients in the TZP arm. To combat this, we matched on presence of hypotension during the treatment period and baseline severity of illness. Finally, it is unclear if the nephrotoxic potentials of the beta-lactam agents are similar. Due to the timeframe of this study, no patients received piperacillin monotherapy which precludes any inference regarding the additional nephrotoxic potential of tazobactam. Further prospective studies of combination antimicrobial chemotherapy are warranted, as are animal and human studies of the mechanism for increased nephrotoxicity.

Conclusion

AKI rate between piperacillin-tazobactam and ampicillin-sulbactam were similar in our large matched cohort study. Additionally, concomitant vancomycin exposure was associated with significant increases in AKI incidence. The magnitude of increase was significantly different for the patients receiving piperacillin-tazobactam when compared to those receiving ampicillin-sulbactam.

Tables and Figures

Table 4.1: Patient demographics among matched cohort

| Variable | SAM (N=612) | TZP (N=1,836) | p |
|--|---------------------|---------------------|----------|
| Age (median [IQR]) | 52 (42-62) | 53 (40-63) | 0.7 |
| Male Gender | 338 (55.2%) | 954 (52.0%) | 0.2 |
| Caucasian Race | 554 (90.5%) | 1,648 (89.8%) | 0.6 |
| Weight, kg (mean[SD]) | 79.9 (22.4) | 80.5 (23.8) | 0.8 |
| BMI (mean[SD]) | 27.7 (7.0) | 27.8 (8.8) | 0.9 |
| CCI (median [IQR]) | 5 (2-9) | 4 (1-9) | 0.002 |
| Initial CrCl (median [IQR]) | 100 (77.8-127.5) | 103.9 (76.8-130.9) | 0.4 |
| Initial CrCl (mL/min) | | | 0.8 |
| 30-59 | 64 (10.5%) | 181 (9.9%) | |
| 60-89 | 165 (27.0%) | 482 (26.3%) | |
| ≥90 | 383 (62.6%) | 1,173 (63.9%) | |
| Hypotension | 42 (6.9%) | 144 (7.8%) | 0.5 |
| Comorbidities | | | |
| Diabetes | 119 (19.4%) | 336 (18.3%) | 0.6 |
| Heart Failure | 28 (4.6%) | 56 (3.1%) | 0.1 |
| Hypertension | 267 (43.6%) | 779 (42.4%) | 0.6 |
| Concomitant nephrotoxic agents | | | |
| Aminoglycoside | 17 (2.8%) | 36 (2.0%) | 0.3 |
| Amphotericin B | 1 (0.2%) | 3 (0.2%) | 1 |
| ACE inhibitor | 88 (14.4%) | 217 (11.8%) | 0.1 |
| ARB | 25 (4.1%) | 59 (3.2%) | 0.4 |
| IV Contrast | 20 (3.3%) | 107 (5.8%) | 0.02 |
| Loop diuretic | 92 (15.0%) | 242 (13.2%) | 0.3 |
| NSAID | 106 (17.2%) | 294 (16.0%) | 0.5 |
| Calcineurin inhibitors | 21 (3.4%) | 57 (3.1%) | 0.8 |
| Vancomycin | 128 (20.9%) | 397 (21.6%) | 0.7 |
| Vasopressors | 4 (0.7%) | 12 (0.7%) | 1 |
| Beta-lactam duration of therapy (days; median [IQR]) | 4 (2-5) | 4 (3-6) | <0.00001 |
| Vancomycin duration of therapy (days; median [IQR]) | (N=128) 7 (4-11) | (N=397) 7 (4-13) | 0.6 |

Table 3.1 footnote:

Data are N(%) unless specified otherwise. ACE – angiotensin converting enzyme; ARB – Angiotensin II receptor blocker; IQR – interquartile range; NSAID – nonsteroidal anti-

inflammatory drug; TZP – piperacillin-tazobactam; SAM – Ampicillin-sulbactam; SD – standard deviation

Table 4.2: Primary outcome

| Outcome | SAM | TZP | p-value |
|----------------|------------|--------------|----------------|
| AKI | 56 (9.15%) | 209 (11.38%) | 0.14 |
| Risk | 48 (7.84%) | 159 (8.66%) | |
| Injury | 7 (1.14%) | 27 (1.47%) | |
| Failure | 1 (0.16%) | 23 (1.25%) | |

Table 2.2 footnote:

AKI – acute kidney injury; TZP – piperacillin-tazobactam; SAM – ampicillin-sulbactam; Risk: \geq 25% decrease in CrCl; Injury: \geq 50% decrease in CrCl; Failure: \geq 75% decrease in CrCl

Table 4.3: Differences in AKI stratified by vancomycin exposure for patients treated with piperacillin-tazobactam or ampicillin-sulbactam

| Outcome | SAM (N=484) | TZP (N=1,439) | p- value | SAM+VA N (N=128) | VAN+TZP (N=397) | p-value |
|----------------|------------------------|--------------------------|---------------------|---------------------------------|----------------------------|----------------|
| AKI | 43 (8.9%) | 137 (9.5%) | 0.74 | 13 (10.2%) | 72 (18.1%) | 0.038 |
| Risk | 38 (7.8%) | 112 (7.8%) | | 10 (7.8%) | 47 (11.8%) | |
| Injury | 4 (0.8%) | 15 (1.0%) | | 3 (2.3%) | 12 (3.0%) | |
| Failure | 1 (0.2%) | 10 (0.7%) | | 0 (0%) | 13 (3.3%) | |

Table 3.3 footnote:

AKI – acute kidney injury; TZP – piperacillin-tazobactam; SAM – ampicillin-sulbactam; VAN – vancomycin; Risk: $\geq 25\%$ decrease in CrCl; Injury: $\geq 50\%$ decrease in CrCl; Failure: $\geq 75\%$ decrease in CrCl

Table 4.4: Bivariate and Multivariate AKI associations

| Variable | Bivariate | | | Multivariate | | |
|--|-------------|--------------|--------------|--------------|-------------|--------------|
| | OR | 95% CI | p | aOR | 95% CI | p |
| <i>Treatment characteristics</i> | | | | | | |
| Treatment group | | | | | | |
| TZP | (reference) | | | (reference) | | |
| SAM | 0.93 | 0.64 – 1.32 | 0.678 | 0.87 | 0.59 – 1.25 | 0.465 |
| SAM+VAN | 1.07 | 0.56 – 1.89 | 0.815 | 0.88 | 0.44 – 1.61 | 0.691 |
| VAN+TZP | 2.11 | 1.54 – 2.86 | <0.001 | 1.77 | 1.26 – 2.46 | 0.001 |
| Duration of beta-lactam therapy (per day increase) | 1.12 | 1.08 – 1.16 | <0.001 | 1.08 | 1.04 – 1.12 | <0.001 |
| <i>Patient characteristics</i> | | | | | | |
| Age (per year increase) | 1 | 0.99 – 1.01 | 0.875 | | | |
| CCI (per point increase) | 1.01 | 0.98 – 1.04 | 0.348 | | | |
| Male gender | 1.19 | 0.92 – 1.54 | 0.187 | | | |
| Caucasian race | 1.14 | 0.75 – 1.81 | 0.57 | | | |
| Baseline creatinine clearance (mL/min) | | | | | | |
| 30-59 | (reference) | | | (reference) | | |
| 60-59 | 0.59 | 0.36 – 0.98 | 0.039 | 0.64 | 0.38 – 1.10 | 0.1 |
| ≥90 | 1.15 | 0.76 – 1.80 | 0.521 | 1.55 | 1.00 – 2.50 | 0.062 |
| Heart failure | 2.52 | 1.45 – 4.18 | 0.001 | 2.06 | 1.11 – 3.66 | 0.016 |
| Diabetes | 1.39 | 1.02 – 1.88 | 0.034 | 1.32 | 0.94 – 1.83 | 0.104 |
| Hypertension | 1.12 | 0.87 – 1.45 | 0.374 | | | |
| Hypotension [†] | 2.05 | 1.37 – 3.00 | <0.001 | | | |
| <i>Concomitant nephrotoxins</i> | | | | | | |
| Aminoglycoside | 2.76 | 1.40 – 5.10 | 0.002 | 1.89 | 0.88 – 3.78 | 0.086 |
| Amphotericin B | 2.75 | 0.14 – 21.59 | 0.381 | | | |
| ACE inhibitor | 1.24 | 0.85 – 1.77 | 0.239 | | | |
| ARB | 0.51 | 0.18 – 1.15 | 0.151 | | | |
| IV Radiocontrast Dye | 0.94 | 0.50 – 1.63 | 0.826 | | | |
| Loop diuretic | 3.59 | 2.68 – 4.79 | <0.001 | 3.06 | 2.22 – 4.19 | <0.001 |
| Calcineurin inhibitor | 3.44 | 2.02 – 5.65 | <0.001 | 4.28 | 2.42 – 7.35 | <0.001 |
| NSAID | 0.79 | 0.54 – 1.12 | 0.2 | | | |
| Vasopressor | 2.77 | 0.77 – 8.02 | 0.079 | | | |

Table 3.4 footnote:

AKI – acute kidney injury; ACE – angiotensin converting enzyme; aOR – adjusted odds ratio;
ARB – angiotensin II receptor antagonist; CCI – Charlson Comorbidity Index; CI – confidence
interval; NSAID – nonsteroidal anti-inflammatory drug; OR – odds ratio; TZP – piperacillin-
tazobactam; SAM – ampicillin-sulbactam; VAN – vancomycin;

†Hypotension removed during AIC minimization step of multivariate analysis

Chapter 5: Predicting AKI in patients treated with empiric antimicrobial therapy with machine learning

Background

Acute kidney injury (AKI) is associated with significant morbidity and mortality.(61) There are a variety of causes and mechanisms for AKI. One common cause of AKI is vancomycin (VAN), which is a glycopeptide antibiotic active against gram-positive bacteria, such as *Staphylococcus aureus*.(62) Vancomycin-related AKI is a well-defined, with incidence ranging from 5 to 43% in a variety of patients.(62) There is a wide variation in the incidence of VAN-associated AKI due to study differences, such as patient population examined, historical dosing strategies, and impurities in early drug formulations. Contemporary literature suggests that approximately 21% of critically ill patients treated with VAN will develop AKI(63), compared to approximately 14% of adult internal medicine patients.(64)

Recent literature implicates concomitant VAN and piperacillin-tazobactam (TZP) therapy in the increased incidence of AKI.(64) Piperacillin-tazobactam is a beta lactam/beta-lactamase inhibitor combination that has antimicrobial activity against many gram-negative pathogens, including *Pseudomonas*, and anaerobic pathogens. Piperacillin-tazobactam is generally considered safe with AKI incidence less than 1% in approval studies; however, the package insert does list acute renal failure as a possible serious adverse effect.(10) This finding has been reproduced many times with AKI incidence in patients treated with VAN+TZP ranging from 9.5 to 34.8%.(17,23,24,33,34,65,66) Additionally, VAN+TZP has been shown to have higher AKI incidence compared to cefepime combined with VAN.(24,66) Despite these findings, no literature has examined the problem of predicting which patients receiving combination antimicrobial therapy are at risk for AKI. While statistical models have been developed in previous studies, these approaches have been limited to covariates that are known confounders.

Machine learning is gaining popularity in bioinformatics in several areas, such as omics, biomedical imaging, and biomedical signal processing.(67) Different techniques are better suited for each field of bioinformatics; however, there are many opportunities to utilize different techniques to represent the data. For example, convolutional neural networks have been utilized successfully in biomedical image processing but recurrent neural networks can be used as many images have a sequential component.(67) Recently, recurrent neural networks were utilized to predict onset of heart failure from electronic medical record data.(68) The model generated in this study outperformed the traditional machine learning approaches in accuracy. This study demonstrates the feasibility of applying complex deep learning techniques to sequential electronic medical record data.

The objective of this study was to predict AKI in patients receiving combination empiric antimicrobial therapy via a variety of machine-learning models. This was done to include a large variety of variables and account for non-linear relationships, which would be difficult to do in a statistical model.

Methods

Patient population

This was a retrospective cohort study of patients at the University of Kentucky Medical Center who received vancomycin (VAN) in combination with piperacillin-tazobactam (TZP), cefepime (CFP), or meropenem (MEM) for at least 48 hours. All patients, 18 years of age and older admitted between July 1, 2008 and June 30, 2017 at the University of Kentucky HealthCare enterprise were eligible for inclusion. While data is available for some situations starting in 2006, the most reliable data is present from 2008 and on. In contrast to previous studies on this topic, patients with previous renal disease (defined by ICD-9 or ICD-10 codes) were eligible for inclusion. Patients were grouped based on the beta-lactam agent utilized for therapy. In cases of multiple course of combination therapy, only the first encounter is included in the analysis.

Data

Patient-specific data was collected from the University of Kentucky Enterprise Data Trust (EDT). The EDT is a large relational database containing a copy of the electronic medical record from UK HealthCare. Data, updated nightly, is available since 2006 and includes: demographics (age, gender, marital status, race); financial classification; provider-level detail (service); medical diagnoses (ICD 9 and ICD 10); medical procedures (inpatient facility and technical procedures, CPT codes); lab tests and results (chemistry, coagulation, hematology, urinalysis, etc.); medications received; visit details (age at visit, length of stay, financial classification, service unit, weekend admission); and vital signs (height, weight, BMI, direct arterial blood pressure, noninvasive blood pressure, heart rate, pulse oximetry, respiratory rate, temperature, death status, tobacco status).

Data collected included gender, age, race, transfer from outside facility, ICU status on admission, laboratory values obtained throughout admission, height and weight on admission, hospital and ICU length of stay, antibiotic dose, antibiotic blood levels, duration of therapy, medical diagnoses, and all lab tests and results. Vital signs throughout hospital stay, mechanical ventilation status, history of cardiac arrest, and mental status (via Glasgow Coma Scale) on admission were collected. Patient data were aggregated on an encounter-day level. Categorical data was converted to binary indicator variables via one-hot encoding. Features were selected from the EHR in the 72 hours prior to the index date.

Data analysis

The primary outcome of this study was empirical antibiotic therapy associated AKI as determined by the risk, injury, failure, loss, and end-stage (RIFLE) criteria.⁽¹⁹⁾ To determine changes in renal function, creatinine clearance was calculated by the adjusted Cockcroft-Gault equation.⁽⁴⁵⁾ The first creatinine clearance obtained during the hospital admission was used as the patient's baseline renal function. Patient index dates were set to 48 hours after the initiation of

combination therapy. To mimic application of predictive models in a real-world setting, data occurring prior to the index date were included in the predictive models. As the majority of patients had less than 5 days of pre-index data, initial models used only data from the 3 days prior to index date.

Basic descriptive statistics for the entire cohort and each therapy group were performed. Continuous data were compared with ANOVA or Kruskal-Wallis tests while categorical data were compared with chi-square tests. Bivariable logistic regression was performed to analyze associations of treatment group with AKI incidence.

Data were separated into training and validation datasets in a 95:5 ratio, the training dataset was then partitioned into a 90:10 split for model training and testing. Models examined included: Naïve Bayes classifier, Random Forest classifier, L2-regularized logistic regression classifier, and Neural Network models. All models were repeated 100 times with different training/test splits. Random selection of outcome was used as a baseline to demonstrate model effectiveness.

In total four neural network models were evaluated. All neural network models relied on the rectified linear unit activation (ReLU) function for hidden layers and a softmax activation function for the output layer. The ReLU function returns all positive inputs to a node or zero if the input is negative, this was selected to produce only positive outputs. Neural network model 1 (NN1) contains two hidden layers of 100 nodes; NN2 contains three 100-node hidden layers. NN3 contains two hidden layers, the first with 500 nodes, followed by a 100-node layer. NN4 is similar to NN1; however, after each hidden layer, a dropout layer was included to reduce overfitting. These networks were built to test whether increased model capacity (NN1 vs NN2 and NN3) or complexity (NN1 vs NN4) improved results. Neural networks were trained with a maximum of 10 epochs, with an early stopping after 2 epochs of no improvement in validation score.

Model performance was assessed on the validation set and metrics included accuracy, precision, recall, area under the receiver operator curve, and F1 score. In addition to model metrics, the top ten features from random forest and L2-regularized logistic regression classifiers were extracted.

All statistical tests and procedures were performed in R and RStudio.(49,50) Machine learning tasks were completed using Python 3.5.2 (69) , scikit-learn v0.18.1 (70), Keras v 2.0.8 (71) and TensorFlow v 1.3.0.(72)

Results

In total, 29,647 patients were included in this study with 67.2% of patients receiving VAN+TZP, 28.1% receiving VAN+CFP, and 4.7% receiving VAN+MEM. Basic patient demographics and summary statistics are presented in Table 5.1. In summary, the mean age of patients was 53.9 (SD 16.48) years and 57.4% were male. Baseline creatinine clearance was approximately 87.4 (SD 51.3) mL/min. There were significant differences between treatment groups in age; however, each group had similar proportion of elderly patients.

Unadjusted outcomes are shown in Table 5.2. The antimicrobial-associated AKI incidence among all patients was 24.7% and was significantly increased in the VAN+TZP group compared to both VAN+CFP and VAN+MEM (Table 5.3). Rates of inpatient mortality were similar among groups and was 11.3% overall. Median length of hospitalization was 10 days (IQR 5-20 days).

Model metrics are summarized in Table 5.4. All models performed better than random selection (RS) in all metrics, except random forest in recall (RF 0.170 [0.166-0.173] vs RS 0.255 [0.251-0.261]; $p < 0.0001$; Table 5.5) and F1 score (RF 0.266 [0.261-0.271] vs RS 0.256 [0.252-0.260]; $p = 0.93$).

The most accurate model in the validation cohort was NN 4 (79.8% [95% CI 79.6 to 80.1%; Figure 5.2), which is expected with the addition of dropout layers to the model

architecture. Naïve Bayes classifier was the least accurate of the models (64.1% [63.9 to 64.4%], $p < 0.0001$ for pairwise comparisons). NN 1, 2, and 3 had similar accuracy rates. Results in the precision metric were similar to that of accuracy (Figure 5.3).

Naïve Bayes classifier demonstrated significantly highest recall when compared to other models (0.593 [0.588 to 0.598], $p < 0.0001$ for all pairwise comparisons; Figure 5.4). Among the neural network models, NN 3 had the highest recall (0.479 [0.463-0.495]) and NN 4 had the lowest recall (0.398 [0.387-0.410], $p < 0.0001$ for pairwise comparisons between other neural networks). Recall was statistically similar between NN 1 and 2.

Neural Network 3 performed the best in terms of AUC under the receiver operating curve (0.683 [0.678-0.687]; Figure 5.5); however, this result was not statistically different from the results from NN1 (0.679 [0.675-0.683], $p = 0.4$) and NN2 (0.678 [0.674-0.682], $p = 0.28$). NN 4 performed significantly worse in AUC compared to other neural network models and had similar performance to L2 logistic regression. Results for F1 followed similar trends to AUC (Figure 5.6), with NN3 performing the best but not having significant differences from NN1 and NN2. The maximum F1 score of 0.521 (0.513-0.529) suggests that further work is need to optimize the models prior to production.

The top ten features from L2 regression and random forest classifiers are shown in Table 5.6. Common features between the models included GFR estimates on index date and serum creatinine measurements. Amphotericin B administration on index date was included in the L2 model, while TZP was included in the random forest model.

Discussion

In this large retrospective review of patients receiving empiric combination antimicrobials, AKI occurred in 24.7% of patients. This is the largest study of this topic to date. Without adjustment for confounders, AKI was significantly more likely in patients who received the combination of vancomycin and piperacillin-tazobactam compared to either cefepime or

meropenem and vancomycin. Interestingly, we found that patients who receive meropenem and vancomycin were more likely to experience AKI than those who received cefepime. This may be due to increased severity of illness amongst the meropenem cohort as this difference was not noted in a smaller retrospective study.(73)

We successfully utilized a variety of machine learning methods to predict AKI in these patients using the data available at 48 hours of therapy. This was primarily done to simulate the use of these findings as a clinical decision support tool to help determine the likelihood of AKI. While the f1 measures of the models were not optimal, the models were still able to predict AKI with only 72 hours of clinical data and may represent a viable clinical tool to inform physician decision making. Model accuracy may improve with longer lookback periods, the inclusion of outpatient data, or the use of more sophisticated methods.

There are several limitations of this study. While the observed AKI incidence was similar to previous studies in this area, we did not attempt to control for confounders while presenting the AKI incidence between different treatment groups. This was done primarily due to the intent of our study being to develop a predictive model rather than examine the established link between increased AKI and VAN+TZP therapy. Another significant limitation is the conversion of numeric variables to categorical variables to account for data missingness. The conversion to a categorical data point allowed the model to evaluate if not ordering a lab or test had significant associations with AKI occurring at a later time point. While this allowed for the investigation of missing lab values, it does increase the sparsity of data, which may limit the interpretation of our results. Receipt of specific medications were treated as binary variables on the patient-day level. This limits inferences surrounding increasing dosing intensity and increased AKI incidence. However, in previous research sensitivity analyses demonstrated that this binary treatment of medication administration did not perform significantly worse at predicting AKI in statistical models than using number of doses or dose amounts. While we included patients with significant

baseline renal impairment, the definition for baseline creatinine clearance may mask AKI in patients with low baseline values.

In conclusion, AKI continues to be an important adverse effect associated with combination antimicrobial therapy. Specifically, vancomycin in combination with piperacillin-tazobactam continues to have higher AKI rates than either cefepime or meropenem when combined with vancomycin. Machine learning models performed well in testing and training dataset. Further work to optimize these models for this data is needed prior to implementation.

Tables and Figures

Table 5.1: Patient demographics

| Variable | Cohort | VAN+CFP | VAN+MEM | VAN+TZP | p-value |
|--|----------------------|----------------------|----------------------|----------------------|---------|
| N | 29,647 | 8,333 | 1,390 | 19,924 | |
| Mean Age (SD) | 53.86 (16.48) | 53.66 (16.5) | 52.12 (17.49) | 54.07 (16.37) | 0.0001 |
| Median Age (IQR) | 55 (42-65) | 55 (42-65) | 54 (39-65) | 55 (43-65) | 0.0008 |
| Age ≥65 | 7,957 (26.8%) | 2,258 (27.1%) | 361 (26.0%) | 5,338 (26.8%) | 0.6 |
| Gender | | | | | <0.0001 |
| Male | 17,027 (57.4%) | 4,567 (54.8%) | 713 (51.3%) | 11,747 (59.0%) | |
| Female | 12,620 (42.6%) | 3,766 (45.2%) | 677 (48.7%) | 8,177 (41.0%) | |
| Baseline CrCl, mL/min [Mean (SD)] | 87.4 (51.3) | 88.5 (51.9) | 96.6 (65.1) | 86.3 (49.9) | <0.0001 |
| Baseline CrCl, mL/min [Median (IQR)] | 81.6 (50.4-115.8) | 82.9 (51.3-117.3) | 84.6 (49.1-127.9) | 80.7 (50.3-114.5) | 0.0001 |

Footnote: N – number, VAN – vancomycin, CFP – cefepime, MEM – meropenem, TZP – piperacillin-tazobactam, SD – standard deviation, IQR – interquartile range, CrCl – creatinine clearance

Table 5.2: Unadjusted outcome results

| Outcome | Cohort | VAN+CFP | VAN+MEM | VAN+TZP | p-value |
|--|--------------|--------------|-------------|--------------|---------|
| Length of hospital stay [mean (SD)] | 16.1 (20.5) | 17.1 (21.1) | 19.7 (29.8) | 15.5 (19.3) | <0.0001 |
| Length of hospital stay [median (IQR)] | 10 (5-20) | 11 (5-21) | 12 (7-22) | 10 (5-19) | <0.0001 |
| Inpatient mortality | 3358 (11.3%) | 981 (11.8%) | 172 (12.4%) | 2205 (11.1%) | 0.1 |
| AKI | 7321 (24.7%) | 1600 (19.2%) | 318 (22.9%) | 5403 (27.1%) | <0.0001 |

Footnote: VAN – vancomycin, CFP – cefepime, MEM – meropenem, TZP – piperacillin-

tazobactam, SD – standard deviation, IQR – interquartile range, AKI – acute kidney injury

Table 5.3: Bivariable odds ratios of AKI among different treatment groups

| VAN+CFP | VAN+MEM | VAN+TZP |
|-----------------|------------------|------------------|
| (ref) | 1.24 [1.09-1.43] | 1.57 [1.47-1.67] |
| 0.80 [0.7-0.92] | (ref) | 1.25 [1.10-1.43] |
| 0.64 [0.6-0.68] | 0.80 [0.7-0.91] | (ref) |

Footnote: VAN – vancomycin, CFP – cefepime, MEM – meropenem, TZP – piperacillin-

tazobactam

Table 5.4: Machine learning model metrics on validation set

| Model | Accuracy | Precision (PPV) | Recall | AUC | F1 Score |
|-------|--------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|
| RS | 0.618 (0.616-0.620) | 0.257 (0.254-0.261) | 0.255 (0.251-0.261) | 0.500 (0.497-0.502) | 0.256 (0.252-0.260) |
| L2 | 0.782 (0.780-0.784) | 0.580 (0.573-0.587) | 0.434 (0.429-0.439) | 0.665 (0.663-0.668) | 0.496 (0.491-0.501) |
| NB | 0.641 (0.639-0.644) | 0.363 (0.359-0.367) | 0.593 (0.588-0.598) | 0.625 (0.622-0.628) | 0.450 (0.446-0.454) |
| RF | 0.768 (0.766-0.770) | 0.618 (0.608-0.629) | 0.170 (0.166-0.173) | 0.568 (0.566-0.570) | 0.266 (0.261-0.271) |
| NN1 | 0.790 (0.787-0.792) | 0.606 (0.595-0.617) | 0.460 (0.446-0.474) | 0.679 (0.675-0.683) | 0.516 (0.509-0.523) |
| NN2 | 0.791 (0.788-0.794) | 0.614 (0.602-0.626) | 0.455 (0.442-0.468) | 0.678 (0.674-0.682) | 0.515 (0.509-0.522) |
| NN3 | 0.785 (0.782-0.788) | 0.593 (0.580-0.605) | 0.479 (0.463-0.495) | 0.683 (0.678-0.687) | 0.521 (0.513-0.529) |
| NN4 | 0.798 (0.796-0.801) | 0.659 (0.648-0.669) | 0.398 (0.387-0.410) | 0.664 (0.660-0.668) | 0.491 (0.484-0.499) |

Footnote: L2 – L2 penalized logistic regression, NB – Naïve Bayes Classifier, NN – Neural

Network, RF – Random Forest Classifier, RS – Random Selection

Table 5.5: Pairwise t-test p-values for model metrics

| Accuracy | | | | | | | |
|-----------|---------|---------|---------|---------|---------|---------|---------|
| Model | L2 | NB | NN1 | NN2 | NN3 | NN4 | RF |
| NB | <0.0001 | | | | | | |
| NN1 | <0.0001 | <0.0001 | | | | | |
| NN2 | <0.0001 | <0.0001 | 0.47 | | | | |
| NN3 | 0.08 | <0.0001 | 0.04 | 0.01 | | | |
| NN4 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | | |
| RF | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | |
| RS | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Precision | | | | | | | |
| Model | L2 | NB | NN1 | NN2 | NN3 | NN4 | RF |
| NB | <0.0001 | | | | | | |
| NN1 | 0.00 | <0.0001 | | | | | |
| NN2 | <0.0001 | <0.0001 | 0.49 | | | | |
| NN3 | 0.24 | <0.0001 | 0.23 | 0.01 | | | |
| NN4 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | | |
| RF | <0.0001 | <0.0001 | 0.24 | 0.51 | 0.0010 | <0.0001 | |
| RS | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Recall | | | | | | | |
| Model | L2 | NB | NN1 | NN2 | NN3 | NN4 | RF |
| NB | <0.0001 | | | | | | |
| NN1 | 0.003 | <0.0001 | | | | | |
| NN2 | 0.017 | <0.0001 | 0.496 | | | | |
| NN3 | <0.0001 | <0.0001 | 0.017 | 0.004 | | | |
| NN4 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | | |
| RF | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | |
| RS | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| AUC | | | | | | | |
| Model | L2 | NB | NN1 | NN2 | NN3 | NN4 | RF |
| NB | <0.0001 | | | | | | |
| NN1 | <0.0001 | <0.0001 | | | | | |
| NN2 | <0.0001 | <0.0001 | 1 | | | | |
| NN3 | <0.0001 | <0.0001 | 0.40 | 0.28 | | | |
| NN4 | 1 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | | |
| RF | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | |
| RS | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |

Table 5.5 (continued)

| F1 score | | | | | | | |
|----------|---------|---------|---------|---------|---------|---------|------|
| Model | L2 | NB | NN1 | NN2 | NN3 | NN4 | RF |
| NB | <0.0001 | | | | | | |
| NN1 | <0.0001 | <0.0001 | | | | | |
| NN2 | <0.0001 | <0.0001 | 0.93 | | | | |
| NN3 | <0.0001 | <0.0001 | 0.93 | 0.93 | | | |
| NN4 | 0.93 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | | |
| RF | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | |
| RS | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.93 |

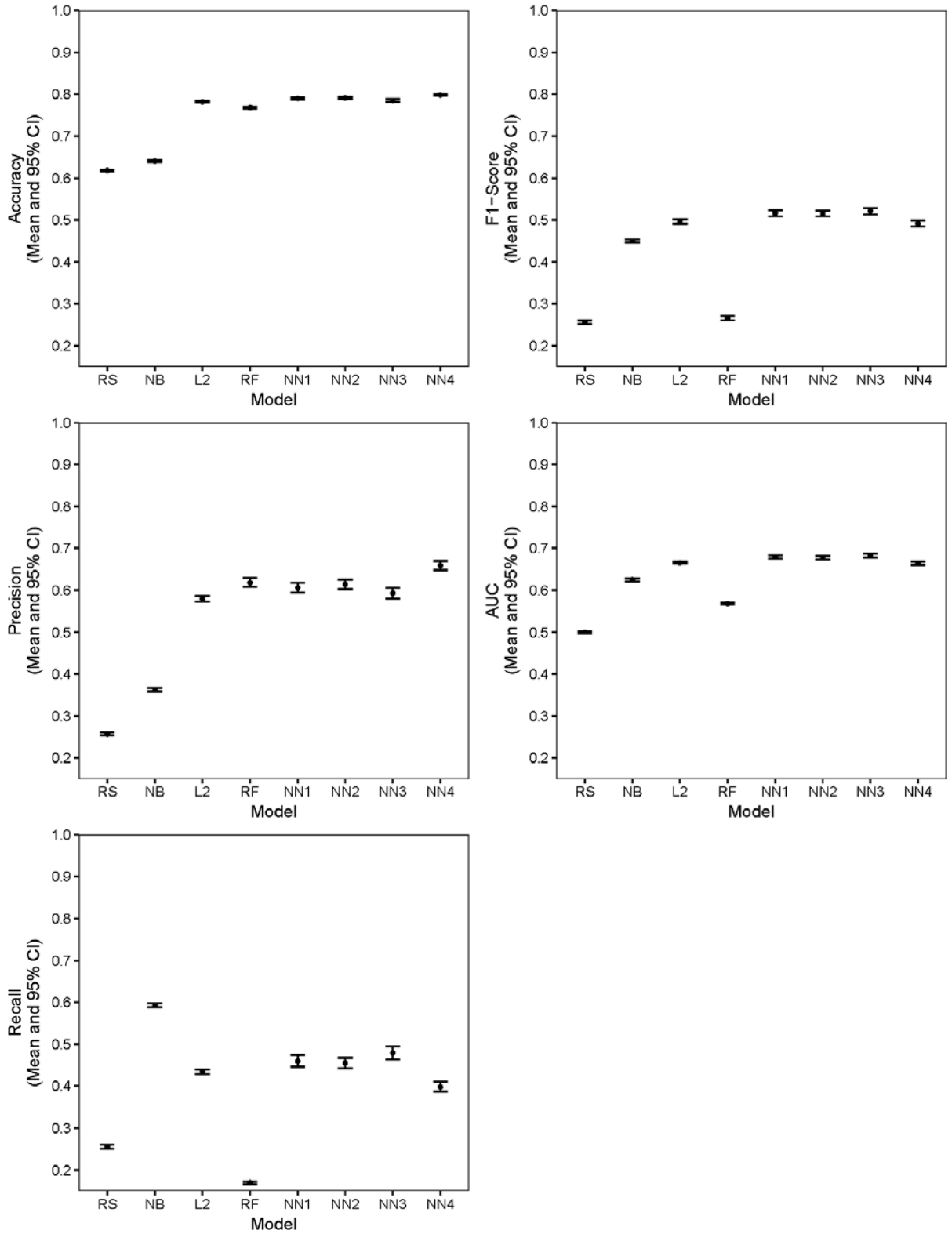
Footnote: L2 – L2 penalized logistic regression, NB – Naïve Bayes Classifier, NN – Neural Network, RF – Random Forest Classifier, RS – Random Selection

Table 5.6: Top ten features in RF and L2 models

| L2 regularized logistic regression | Random forest |
|--|-------------------------------|
| Urine Casts ordered on T-1 | Baseline CrCl |
| GFR if African American on T0 | GFR if African American on T0 |
| Serum IgE on T-2 | GFR on T0 |
| Serum Creatinine on T0 | Serum Creatinine on T0 |
| Urine Creatinine on T0 | Oxygen saturation on T0 |
| MRI Upper Extremity Joint with and without IV Contrast Left on T-1 | Age |
| Amikacin Trough ordered on T-1 | TZP given on T-1 |
| GFR on T0 | Serum Phosphorus on T0 |
| Amphotericin B given on T0 | RBC Count on T0 |
| Liver Abscess/Cyst percutaneous drainage on T0 | TZP given on T0 |

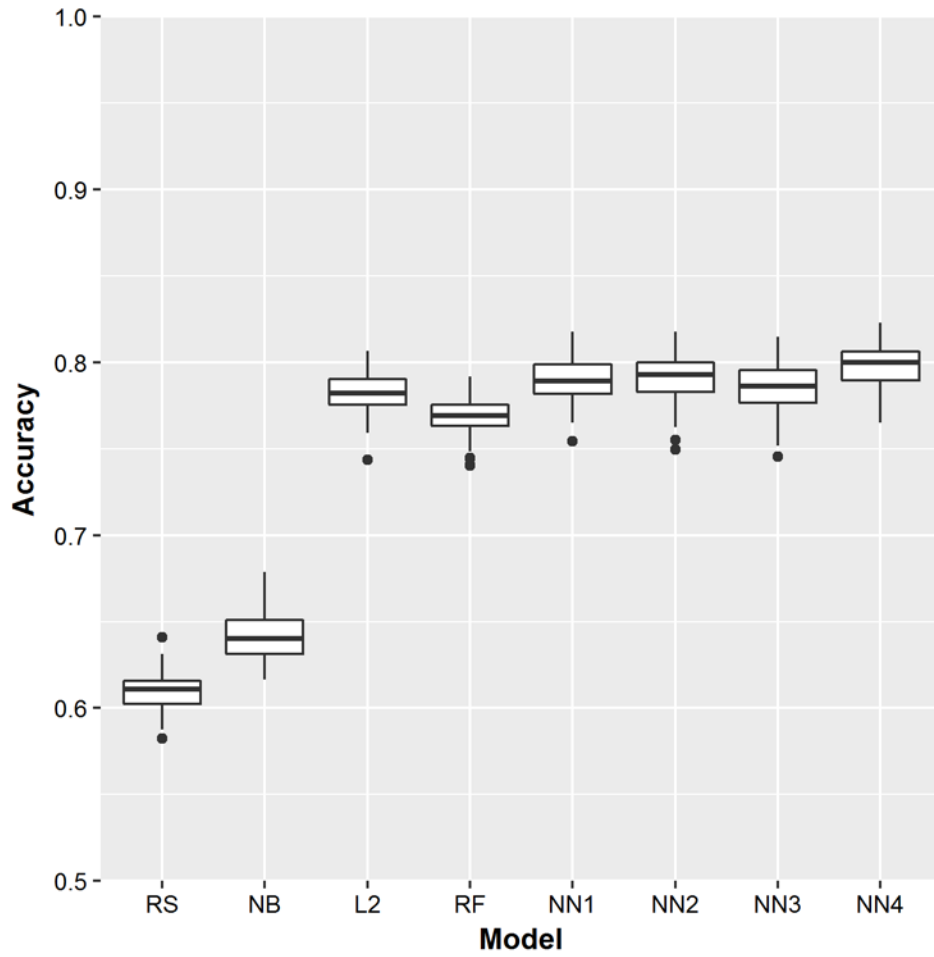
Footnote: T0 – index date, T-1 – index date – 1, T-2 – index date -2, TZP – piperacillin-tazobactam, GFR – glomerular filtration rate (estimated by MDRD equation), RBC – red blood cell, CrCl – creatinine clearance, IgE – Immunoglobulin E

Figure 5.1: Model metrics mean and 95% confidence interval visualized



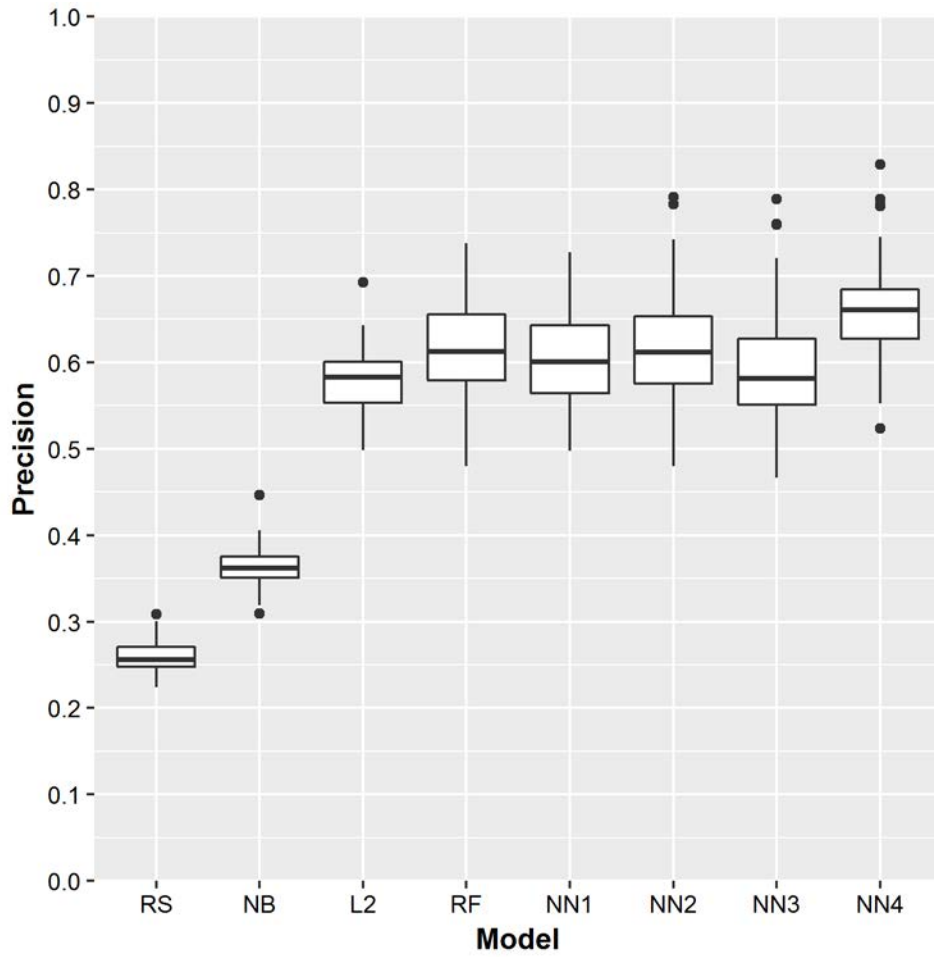
Footnote: L2 – L2 penalized logistic regression, NB – Naïve Bayes Classifier, NN – Neural Network, RF – Random Forest Classifier, RS – Random Selection

Figure 5.2: Comparison of accuracy between models



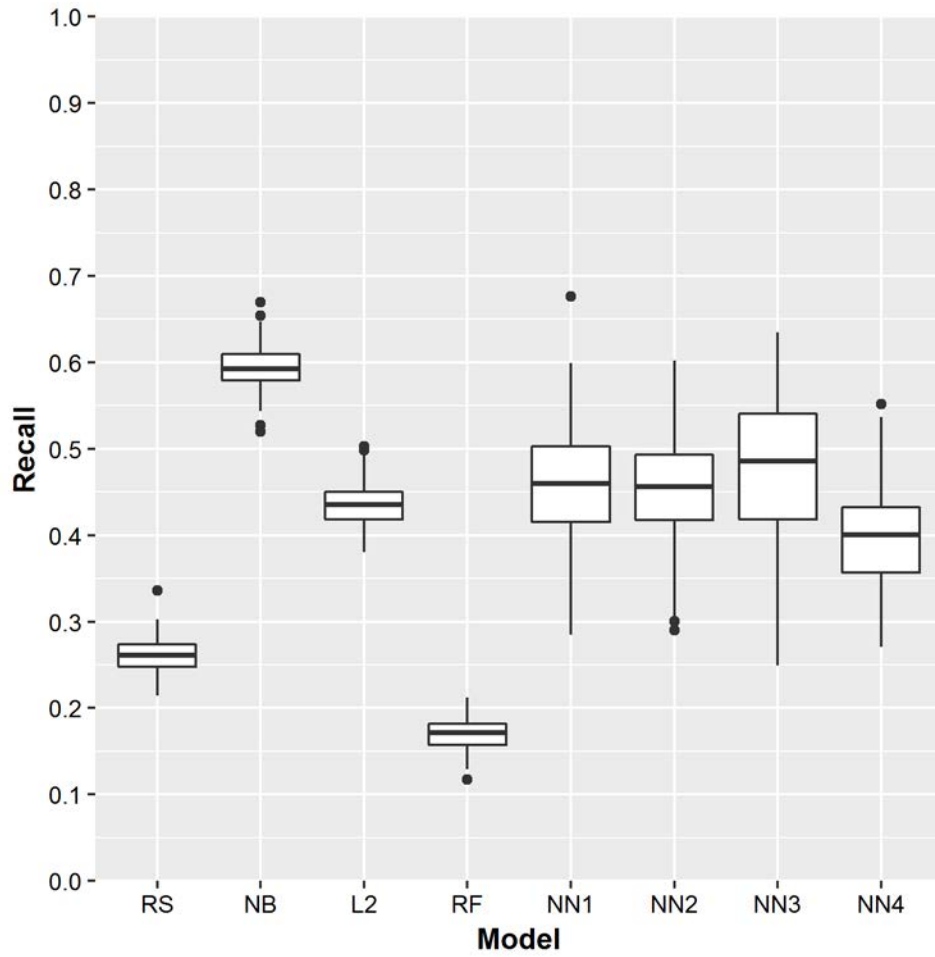
Footnote: Note Y-axis scale. L2 – L2 penalized logistic regression, NB – Naïve Bayes Classifier, NN – Neural Network, RF – Random Forest Classifier, RS – Random Selection

Figure 5.3: Comparison of precision between models



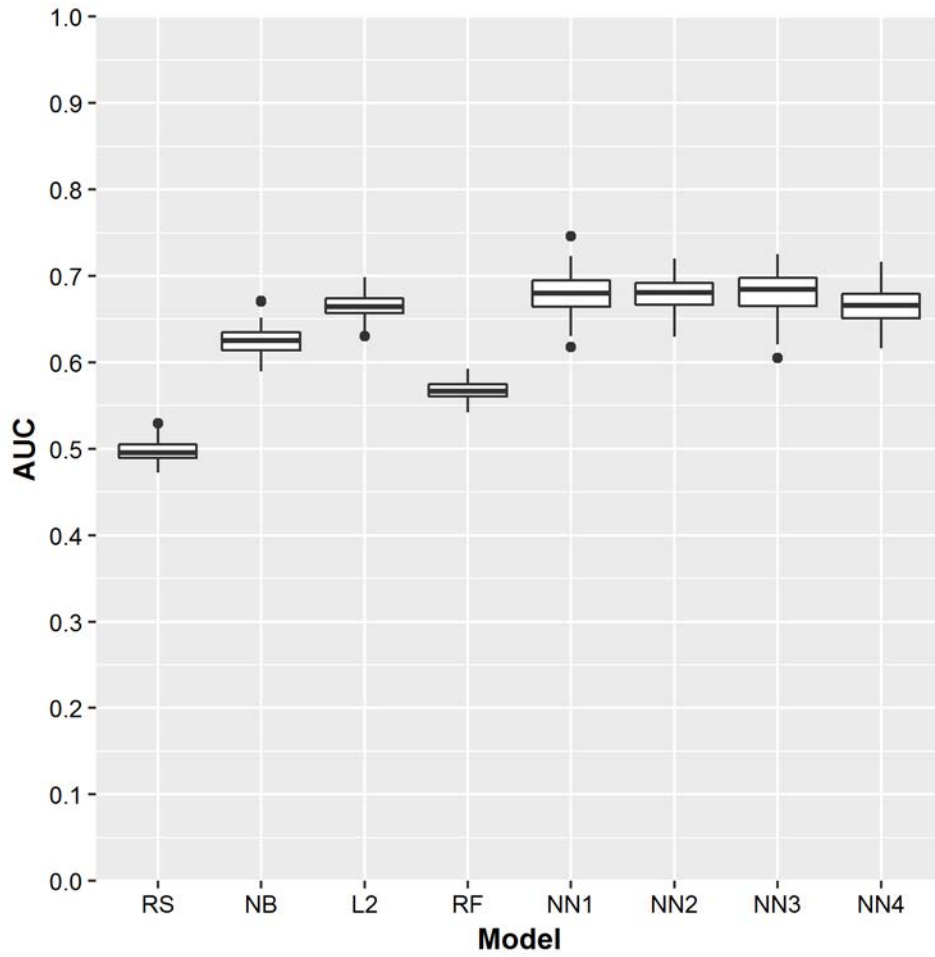
Footnote: L2 – L2 penalized logistic regression, NB – Naïve Bayes Classifier, NN – Neural Network, RF – Random Forest Classifier, RS – Random Selection

Figure 5.4: Comparison of recall between models



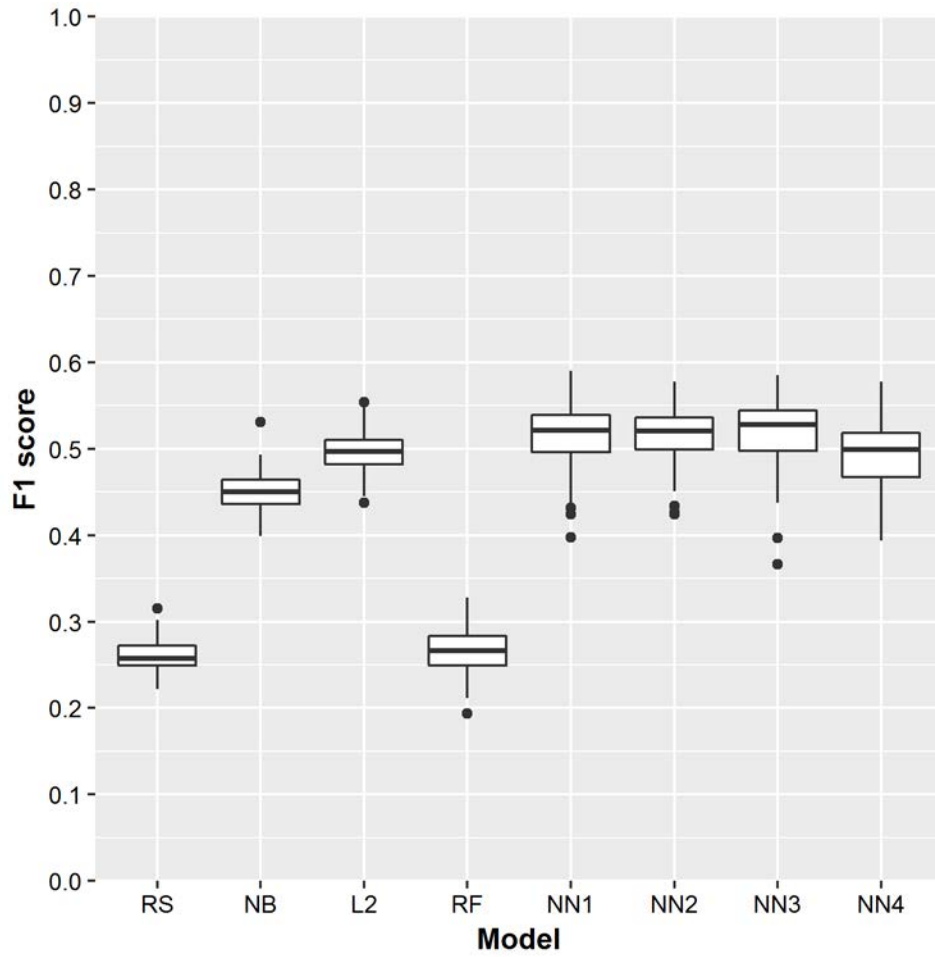
Footnote: L2 – L2 penalized logistic regression, NB – Naïve Bayes Classifier, NN – Neural Network, RF – Random Forest Classifier, RS – Random Selection

Figure 5.5: Comparison of AUC between models



Footnote: L2 – L2 penalized logistic regression, NB – Naïve Bayes Classifier, NN – Neural Network, RF – Random Forest Classifier, RS – Random Selection

Figure 5.6: Comparison of F1 score between models



Footnote: L2 – L2 penalized logistic regression, NB – Naïve Bayes Classifier, NN – Neural Network, RF – Random Forest Classifier, RS – Random Selection

Chapter 6: Conclusions and Future Directions

Conclusions

The presented research clearly demonstrates an association between AKI and combination therapy with VAN and TZP. While this finding is certainly not novel, as shown by the volume of literature reviewed in Chapter 1, the studies presented are among the largest in terms of sample population. Additionally, a common definition of AKI was shared among the studies, allowing for comparisons of findings between studies.

Chapter 2 demonstrates a significant difference in AKI incidence between VAN+TZP and VAN+CFP. While this difference was demonstrated in previous literature, this study leveraged the large sample size to control for a variety of confounders and presents a robust association between VAN+TZP and AKI.

From available literature, it was unclear if VAN+TZP was more nephrotoxic when compared to non-CFP agents. Chapter 3 presents the most robust study of VAN+TZP compared to VAN+MEM. The results clearly show an increase in AKI incidence observed in the VAN+TZP cohort. This is a valuable finding as MEM and TZP have similar bacterial spectra and clinical indications. Further research into the comparisons of TZP alternatives are warranted. For example, CFP and MEM should be compared directly to determine if either agent possesses a significant advantage over the other in regards to renal disease.

Previous literature failed to investigate a potential mechanism for the observed increase in renal insult with TZP compared to other beta-lactam agents. Chapter 4 presents the novel investigation of the impact of the addition of beta-lactamase inhibitors on nephrotoxicity. Results suggest that the addition of a second beta-lactam-like agent is not the mechanism for increased AKI seen with TZP. Interestingly, the addition of VAN to either agent resulted in increased AKI incidence; however, the magnitude of AKI increase was significantly larger in the TZP cohort.

In summary, Chapters 2 through 4 clearly demonstrate a need for antimicrobial stewardship interventions related to the use of empiric combination broad-spectrum antibiotics. A proposed stewardship tool is the 48-hour antibiotic timeout, in which the multidisciplinary care team reviews a patient's history and determines an appropriate course of therapy based on the available data. Chapter 5 proposes the use of machine learning algorithms as a clinical decision support tool at 48 hours of therapy. Neural network models appear to have an advantage in predicting future AKI events from the data presented. While further optimization may increase the model utility, the presented models can still provide valuable information to providers.

Future Directions

While the literature continues to evolve in this field, several knowledge gaps remain. A continued focus in identifying AKI-associated risk factors in special populations is needed. In the critically ill population, only one published study of AKI incidence among patients receiving VAN+TZP and VAN+CFP exists.(28) The results of this evaluation were inconclusive due to small sample size, but suggest that no difference in AKI incidence exists between these combinations. This finding is discordant with the body of literature that demonstrates significant differences in AKI incidence and propensity.

Cystic fibrosis patients exhibit altered pharmacokinetics and pharmacodynamics and as such may respond differently to nephrotoxins.(74,75) These metabolic alterations have been controlled for in other fields of research through stratification of patients by cystic fibrosis status.(76) One important potential confounder in our cystic fibrosis population is the utilization of extended infusion beta-lactam therapy. Specific dosing protocols for extended infusion antibiotics did not exist in our institution until fairly recently and it is difficult to ascertain clinical reasoning behind the decision to utilize extended infusion previously. However, all studies currently published examining AKI incidence among different beta-lactam infusion strategies

have shown no statistically meaningful differences.(33–36) Additional considerations include high utilization of aminoglycoside antibiotics, long-term hospitalizations, and frequent exposure to the healthcare system.

People who inject drugs (PWID) are at higher risk of severe, deep-seeded infections that require long-term antimicrobial therapy. In addition to the need for long-term therapy, PWID tend to be younger and have fewer comorbidities than the population typically represented in the AKI literature. As such, a directed evaluation of empiric combination therapy associated AKI in PWID should be conducted.

The vast majority of studies in this field have been single center retrospective evaluations. This is problematic due to an inability to demonstrate clear causality. Additionally, institution-specific confounders may exist and limit the generalizability of the findings to outside hospitals. Specifically, community hospitals may have difficulty assessing how these findings impact their patient population which tends to be less acutely ill than those of large academic tertiary medical centers.

Our approach to predicting AKI with machine learning models is promising. We were able to predict AKI with approximately 80% accuracy; however, there is still much room for improvement. More sophisticated modeling techniques may improve accuracy significantly. The incorporation of features from medical progress notes can provide additional details into the patients' health status. Leveraging natural language processing and medical ontologies can improve this area.


```

vid<-vanc$Encounter.ID
vid<-vid[!duplicated(vid)]

ptz<-
meds2[meds2$drug =='PTZ',]          ##And piperacillin/
tazobactam
pid<-ptz$Encounter.ID
pid<-pid[!duplicated(pid)]

meds<-
meds2                                ##Cleaning environme
nt and RAM
rm(meds2)

cvp<-
subset(demo, demo$ENCNTR_ID %in% cefid &          ##subsets all patie
nts who received all three drugs for later use
      demo$ENCNTR_ID %in% vid &
      demo$ENCNTR_ID %in% pid)
cv<- subset(demo, demo$ENCNTR_ID %in% cefid          ##all patients
who received ONLY cefepime and vanc
      & demo$ENCNTR_ID %in% vid &
      !(demo$ENCNTR_ID %in% cvp$ENCNTR_ID))
pv<- subset(demo, demo$ENCNTR_ID %in% pid &          ##all patients
who received ONLY PTZ and vanc
      demo$ENCNTR_ID %in% vid &
      !(demo$ENCNTR_ID %in% cvp$ENCNTR_ID))

cv$LENGTH_OF_STAY_NUM<-
as.numeric(cv$LENGTH_OF_STAY_NUM)          ##Variable cleanup
cv<-subset(cv, cv$LENGTH_OF_STAY_NUM >=2)
pv$LENGTH_OF_STAY_NUM<-as.numeric(pv$LENGTH_OF_STAY_NUM)
pv<-subset(pv, pv$LENGTH_OF_STAY_NUM >=2)

cmeds<-
subset(meds, meds$Encounter.ID %in% cv$ENCNTR_ID)  ##subsetting
the meds for only those received the drugs we care about
pmeds<-subset(meds, meds$Encounter.ID %in% pv$ENCNTR_ID)

source('f:/Jessica data/Test/overlap.R')          ##Load the 'ov
erlap' script which takes a frame of meds and gives a list of those
                                                    ##who received
vancomycin and the drug specified by the drg variable for 2 days

cmeds$date<-
sapply(strsplit(cmeds$Performed.Date.Time, ' '), '[' ,1)      ##clean
ing the meds dataset for the cefepime group
cmeds$time<-sapply(strsplit(cmeds$Performed.Date.Time, ' '), '[' ,2)

```

```

cmeds$ampm<-sapply(strsplit(cmeds$Performed.Date.Time, ' '), '[' ,3)
cmeds$time2<-paste(cmeds$time, cmeds$ampm)
cmeds$time<-cmeds$time2
cmeds$ampm<-NULL
cmeds$time2<-NULL
cmeds$date<-as.Date(cmeds$date, format = "%m/%d/%Y")

pmeds$date<-
sapply(strsplit(pmeds$Performed.Date.Time, ' '), '[' ,1)      ##and t
he PTZ group
pmeds$time<-sapply(strsplit(pmeds$Performed.Date.Time, ' '), '[' ,2)
pmeds$ampm<-sapply(strsplit(pmeds$Performed.Date.Time, ' '), '[' ,3)
pmeds$time2<-paste(pmeds$time, pmeds$ampm)
pmeds$time<-pmeds$time2
pmeds$ampm<-NULL
pmeds$time2<-NULL
pmeds$date<-as.Date(pmeds$date, format = "%m/%d/%Y")

overlap(cmeds, drg='Cefepime')      ##Find the ove
r lap between the cefepime and vancomycin treatment. Takes a while.
overlap(pmeds, drg='PTZ')          ##Same as abov
e for the PTZ. Takes EVEN LONGER... pick up a book.

library(plyr)                       ## load the 'p
lyr' package for access to ldply function which takes a list and
##and outputs
a data fram with variables V1, V2, V3...VN.
cvinc<-
ldply(Cefepime_Vanc_included)      ##Change the list of
EIDs and number of overlap to a dataframe
pvinc<-ldply(PTZ_Vanc_included)

names(cvinc)[names(cvinc)=='V1']<-
'EID'      ##rename V1 to a descriptive variable
names(pvinc)[names(pvinc)=='V1']<- 'EID'

cv2<-
subset(cv, cv$ENCNTR_ID %in% cvinc$EID)      ##subset the cefepi
me patients to those only receiving both drugs for >=2days
pv2<-
subset(pv, pv$ENCNTR_ID %in% pvinc$EID)      ##same as above wit
h PTZ. Using new variables to avoid any unwanted changes

cv2$group<-
'CV'      ##Adding group variable f
or use later. Eventually will merge dataset

```

```

pv2$group<-
'PV'                                ##this variable will main
tain data

cv<-
cv2                                ##Cleaning environ
ment and RAM
pv<-pv2
rm(cv2,pv2,Cefepime_Vanc_included, PTZ_Vanc_included)
cv$AGE<-
as.numeric(cv$AGE)                ##Changing character t
o numeric variable for analysis
pv$AGE<-as.numeric(pv$AGE)

cv<-
subset(cv, cv$AGE >=18)            ##ONLY adults >= 1
8 kept for both groups
pv<-subset(pv, pv$AGE >=18)

cv2<-
subset(cv, !(cv$ADMT_SRC_CD_DES=='HOSPITAL TRANSFER')&!(cv$ADMT_SRC_
CD_DES=='OTHER HEALTH FACIL')    ##Eliminating transfers
&!(cv$ADMT_SRC_CD_DES=="TRANS FM UK GOOD SAM")&!(cv$ADMT
_SRC_CD_DES=="TRANSFER FROM SNF"))

pv2<-
subset(pv, !(pv$ADMT_SRC_CD_DES=='HOSPITAL TRANSFER')&!(pv$ADMT_SRC_
CD_DES=='OTHER HEALTH FACIL')
&!(pv$ADMT_SRC_CD_DES=="TRANS FM UK GOOD SAM")&!(pv$ADMT
_SRC_CD_DES=="TRANSFER FROM SNF"))

cv<-
cv2                                ##Cleaning environ
ment and RAM
pv<-pv2
rm(cv2,pv2, pvinc, cvinc)

labs<-
read.csv('New Labs.csv', colClasses='character')    ##imports
the labs dataset, VERY large
labs$date<-
sapply(strsplit(labs$ENTRD_DT_TM, ' '), '[' ,1)    ##Cleaning dat
a up
labs$time<-sapply(strsplit(labs$ENTRD_DT_TM, ' '), '[' ,2)
labs$ampm<-sapply(strsplit(labs$ENTRD_DT_TM, ' '), '[' ,3)
labs$time2<-paste(labs$time, labs$ampm)
labs$time<-labs$time2
labs$ampm<-NULL
labs$time2<-NULL

```



```

labs$date<-as.Date(labs$date,format = "%m/%d/%Y")

source('f:/Jessica data/Test/first_scr.R')          ##loads 'first
_scr' function which takes the labs data and pulls the first value
                                                    ##and outputs
a list with EID and value number
scr<-
subset(labs, labs$ITEM_NAME=='Creatinine Level') ##subset labs for j
ust the SCr values
firstscr(scr)                                       ##Obtains first
t SCr for the values in the entire labs set.
                                                    ##Consider sub
setting to the labs for the CV and PV groups.
                                                    ##VERY CPU int
ensive. Grab a coffee break. Outputs list 'eid_test2'
scr_list<-ldply(eid_test2)
names(scr_list)[names(scr_list)=='V1']<-
"EID"          ##adding descriptive variable names
names(scr_list)[names(scr_list)=='V2']<-"baseline_scr"

cvscr<-
subset(scr_list, scr_list$EID %in% cv$ENCNTR_ID) ##finding the SCrs
for patients in our datasets
pvscr<-subset(scr_list, scr_list$EID %in% pv$ENCNTR_ID)

names(cv)[names(cv)=='ENCNTR_ID']<-
'EID'          ##changing ENCNTR_ID to EID for merging purposes.
Also, EID is easier to type
names(pv)[names(pv)=='ENCNTR_ID']<-'EID'

cv2<-
merge(cv,cvscr, by="EID")                          ##merge function wi
ll overwrite any data if a mistake is made, so using new variables
pv2<-merge(pv,pvscr, by='EID')

cv<-cv2
pv<-pv2
rm(pv2,cv2, cvscr,pvscr,eid_test2)                  ##cl
eaning environment and RAM. This computer needs more RAM

cvscr<-
subset(scr, scr$ENCNTR_ID %in% cv$EID)              ##subsetting the da
ta for SCr for quicker computing. Reusing variable names from
pvscr<-
subset(scr, scr$ENCNTR_ID %in% pv$EID)              ##before is probabl
y not the best idea

source('f:/Jessica data/Test/maxscr.R')            ##load the 'ma
xscr' function which outputs the list of maximum scr and EID

```

```

maxscr(cvscr)                                ##outputs max_
scr_list, if it is run on the next data set, you lose the data just
generated
c_max_scr_list<-
max_scr_list                                ##this overcomes that
maxscr(pvscr)                                ##rerun the sc
ript on the PTZ data set, takes a little longer
p_max_scr_list<-
max_scr_list                                ##probably not needed but for
consistency purposes

max_cvscr<-
ldply(c_max_scr_list)                        ##converting lists to dat
aframes
max_pvscr<-ldply(p_max_scr_list)

names(max_cvscr)[names(max_cvscr)=='V1']<-
'EID'    ##changing variable names to something that makes sense

names(max_cvscr)[names(max_cvscr)=='V2']<- 'max_scr'
names(max_pvscr)[names(max_pvscr)=='V1']<- 'EID'
names(max_pvscr)[names(max_pvscr)=='V2']<- 'max_scr'

cv2<-
merge(cv,max_cvscr, by='EID', all=T)          ##merging datasets,
all=T is added to preserve any patients with a baseline but no max

pv2<-
merge(pv,max_pvscr, by='EID', all=T)          ##which shouldn't h
appen, but this is just a precaution to maintain the data.

cv<-
cv2
ironment again.                             ##Cleaning the env
pv<-pv2
rm(cv2,pv2,cvscr,pvscr,max_cvscr,max_pvscr,scr,
scr_list, c_max_scr_list,p_max_scr_list, max_scr_list)

cmeds<-
subset(cmeds, cmeds$Encounter.ID %in% cv$EID) ##eliminating data ab
out patients not continuing in the data.
pmeds<-subset(pmeds, pmeds$Encounter.ID %in% pv$EID)

cvp<-
rbind(cv,pv)                                ##The moment we've b
een waiting for! The datasets are merged into one
##It may have b
een able to be merged earlier but now we are really done

```

```

                                                                    ##generating ce
fepime or PTZ specific data from the original sets.
                                                                    ##This also all
ows me to subset the vancomycin use data to only those patients
vanc<-
subset(vanc, vanc$Encounter.ID %in% cvp$EID)  ##we still have in th
e data. Alternatively, I could have created cv and pv specific
                                                                    ##vancomycin da
tasets and rbind'd them together. But this works just as well.
                                                                    ##The vanc data
set will be used in a bit. First, time to generate some more data.

rm(cv,pv)                                                                    ##these exist i
n cvp and are no longer needed.

cvp$baseline_scr<-
as.numeric(cvp$baseline_scr)          ##Changing these character 'numbe
rs' to numeric ones for use!
cvp$max_scr<-as.numeric(cvp$max_scr)
cvp<-subset(cvp, is.na(cvp$baseline_scr)==F)

    ## calculate baseline creatinine clearance for all pts
for(i in 1:length(cvp$EID)){
  if(cvp$GENDER[i]=='FEMALE'){
    cvp$baseline_crcl[i]<- (0.85*((140-
cvp$AGE[i])/cvp$baseline_scr[i]))
  }
  else{
    cvp$baseline_crcl[i]<- ((140-cvp$AGE[i])/cvp$baseline_scr[i])
  }
}

##calculate minimum creatinine clearance for all pts
for(i in 1:length(cvp$EID)){
  if(cvp$GENDER[i]=='FEMALE'){
    cvp$min_crcl[i]<- (0.85*((140-cvp$AGE[i])/cvp$max_scr[i]))
  }
  else{
    cvp$min_crcl[i]<- ((140-cvp$AGE[i])/cvp$max_scr[i])
  }
}

cvp$percent_change<-(cvp$min_crcl/cvp$baseline_crcl-
1)*100          ##calculate percent change from baseline so that decre
ases are negative

for(i in 1:length(cvp$EID)){                                                                    ##
assign RIFLE labels to appropriate degrees of renal impairment

```

```

    if (cvp$percent_change[i]>=0){
if percent_change is >=0, the max SCr is equal to baseline, suggesti
ng GFR improvement
        cvp$RIFLE[i]<-"No injury"
    }
    else {
        if (abs(cvp$percent_change[i])<25){
            cvp$RIFLE[i]<-'No injury'
        }
        if (abs(cvp$percent_change[i])>=25 & abs(cvp$percent_change[i]<
50){
            cvp$RIFLE[i] <- 'RISK'
        }
        if (abs(cvp$percent_change[i])>=50 & abs(cvp$percent_change[i]<
75){
            cvp$RIFLE[i] <- 'INJURY'
        }
        if (abs(cvp$percent_change[i])>=75){
            cvp$RIFLE[i] <- 'Failure'
        }
    }
}

for(i in 1:length(cvp$EID)){
signs binary outcome for AKI (Risk, Injury, Failure) vs No AKI
    if(cvp$RIFLE[i] == 'No injury'){
n convert to a 0/1 answer for modeling.
        cvp$AKI[i]<-"No AKI"
    }
    else{
        cvp$AKI[i]<-'AKI'
    }
}

# Starting here we do a lot of loading scripts

source('f:/Jessica data/Test/first_vanc.R')
ds the first vancomycin trough
vanc<-
rbind(pmeds,cmeds)
mycin dataset with some of the manipulated time variables
vanc<-
subset(vanc, vanc$drug=='Vancomycin')
vanc$Dose<-as.numeric(vanc$Dose)

source('f:/Jessica data/Test/test_avgvanc.R')
calculates the average daily dose of vancomycin for the entire time
on therapy

```

```

for (i in 1:length(vanc$Encounter.ID)){
  standardize the doses in MG instead of G, multiplying 1g by 1000 to
  get 1000 mg
  if(vanc$drug[i]=='Vancomycin'){
    if (vanc$UOM[i]=='gram'){
      vanc$UOM[i] <- 'MG'
      vanc$Dose[i] <- vanc$Dose[i]*1000
    }
  }
}
for (i in 1:length(vanc$Encounter.ID)){
  misdocumented 1g doses
  if(vanc$Dose[i] < 10){
    vanc$Dose[i] <- vanc$Dose[i]*1000
  }
}
test_avgvanc(vanc)
avgvanc outputs Test_Average_vanc_dose_list
avg_vanc<-ldply(Test_Average_vanc_dose_list)
> dataframe
names(avg_vanc)[names(avg_vanc)=='V1']<-
'EID'
names(avg_vanc)[names(avg_vanc)=='V2']<- 'avg_daily_vanc_dose'

cvp<-
merge(cvp,avg_vanc, by='EID', all=T)
cvp$avg_daily_vanc_dose<-
as.numeric(cvp$avg_daily_vanc_dose)
vlabs<-
labs[labs$ITEM_NAME=='Vancomycin Level Trough',]
vlabs<-
subset(vlabs, vlabs$ENCNTR_ID %in% cvp$EID)
vlabs$VAL_NUM<-
as.numeric(vlabs$VAL_NUM)
firstvanc(vlabs)
is first_vanc_list
first_vancdf<-ldply(first_vanc_list)
names(first_vancdf)[names(first_vancdf)=='V1']<-
'EID'
names(first_vancdf)[names(first_vancdf)=='V2']<-
'first_vanc_trough'

```

```

cvp<-
merge(cvp, first_vancdf, by='EID',all=T)          ##first vanc t
rough is added to the dataset

rm(Test_Average_vanc_dose_list, first_vanc_list, first_vancdf, avg_v
anc) ##cleaning RAM

source('f:/Jessica data/Test/maxvanc.R')        ##loads maxvanc
script which finds the maximum vancomycin trough
maxvanc(vlabs)                                  ##output is max_
vanc_list
maxvancdf<-ldply(max_vanc_list)                 ##list--
> dataframe
names(maxvancdf)[names(maxvancdf)=='V1']<-
'EID'      ##renaming variables
names(maxvancdf)[names(maxvancdf)=='V2']<- 'max_vanc_trough'
cvp<-
merge(cvp, maxvancdf, by='EID', all=T)          ##adding max_vanc_tro
ugh to dataset

cvp$first_vanc_trough<-as.numeric(cvp$first_vanc_trough)
cvp$max_vanc_trough<-as.numeric(cvp$max_vanc_trough)

for (i in 1:length(cvp$EID)){                    ##For loop addin
g the vancomycin trough classifications for first vanc trough
  if (is.na(cvp$first_vanc_trough[i])){
    cvp$first_vanc_class[i] <- "No levels"
  }
  if(is.na(cvp$first_vanc_trough[i])==F){
    if (cvp$first_vanc_trough[i]<10){
      cvp$first_vanc_class[i]<- 'subtherapeutic'
    }
    if (cvp$first_vanc_trough[i]>=10 & cvp$first_vanc_trough[i]<15){
      cvp$first_vanc_class[i]<- 'low_therapeutic'
    }
    if (cvp$first_vanc_trough[i]>=15 & cvp$first_vanc_trough[i]<=20)
    {
      cvp$first_vanc_class[i]<- 'high_therapeutic'
    }
    if (cvp$first_vanc_trough[i]>20 ){
      cvp$first_vanc_class[i]<- 'supratherapeutic'
    }
  }
}
}

for (i in 1:length(cvp$EID)){                    ##For loop adding
the vancomycin trough classifications for maximum vanc trough
  if (is.na(cvp$max_vanc_trough[i])){

```

```

    cvp$max_vanc_class[i] <- "No levels"
  }
  if(is.na(cvp$max_vanc_trough[i])==F){
    if (cvp$max_vanc_trough[i]<10){
      cvp$max_vanc_class[i]<- 'subtherapeutic'
    }
    if (cvp$max_vanc_trough[i]>=10 & cvp$max_vanc_trough[i]<15){
      cvp$max_vanc_class[i]<- 'low_therapeutic'
    }
    if (cvp$max_vanc_trough[i]>=15 & cvp$max_vanc_trough[i]<=20){
      cvp$max_vanc_class[i]<- 'high_therapeutic'
    }
    if (cvp$max_vanc_trough[i]>20 ){
      cvp$max_vanc_class[i]<- 'supratherapeutic'
    }
  }
}

cvpmeds<-
rbind(cmeds,pmeds)          ##creating subject specif
ic medication dataset
source('f:/Jessica data/Test/dot.R')      ##load DoT scrip
t which calculates total DOT, DOT for each drug individually, and in
combination
dot(cvpmeds)                ##outputs DOT_li
st, takes quite a while, go get some coffee.
dotdf<-ldply(DOT_list)      ##list--
> dataframe; unlike the other lists-
>dfs, this has 7 variable names to change
names(dotdf)[names(dotdf)=='V1']<- "EID"
names(dotdf)[names(dotdf)=='V2']<-
"Total_DOT"          ##used DOT instead of DoT for ease of typing
names(dotdf)[names(dotdf)=='V3']<- "Vanc_DOT"
names(dotdf)[names(dotdf)=='V4']<- "PTZ_DOT"
names(dotdf)[names(dotdf)=='V5']<- "PTZ_Vanc_DOT"
names(dotdf)[names(dotdf)=='V6']<- "CFP_DOT"
names(dotdf)[names(dotdf)=='V7']<- "CFP_Vanc_DOT"

cvp<-
merge(cvp, dotdf, by='EID',all=T)          ##adding DoT informat
ion into dataset

cvp$Total_DOT<-
as.numeric(cvp$Total_DOT)                ##convert character numbers to
numeric ones for math
cvp$Vanc_DOT<-as.numeric(cvp$Vanc_DOT)
cvp$PTZ_DOT<-as.numeric(cvp$PTZ_DOT)
cvp$PTZ_Vanc_DOT<-as.numeric(cvp$PTZ_Vanc_DOT)
cvp$CFP_DOT<-as.numeric(cvp$CFP_DOT)

```

```

cvp$CFP_Vanc_DOT<-as.numeric(cvp$CFP_Vanc_DOT)

rm(DOT_list,max_vanc_list,maxvancdf,dotdf)          ##cleaning

cvp$Combo_DOT<-
cvp$PTZ_Vanc_DOT+cvp$CFP_Vanc_DOT    ##creates composite combination
tx variable for analysis, needs to be done before next step.

##### sets 0 values to NA so the 0's don't impact any mean, median
calculations... but have to add na.rm=T to most #####
for(i in 1:length(cvp$EID)){
  if (cvp$CFP_DOT[i] == 0){
    cvp$CFP_DOT[i]<-NA
  }
}

for(i in 1:length(cvp$EID)){
  if (cvp$PTZ_DOT[i] == 0){
    cvp$PTZ_DOT[i]<-NA
  }
}

for(i in 1:length(cvp$EID)){
  if (cvp$PTZ_Vanc_DOT[i] == 0){
    cvp$PTZ_Vanc_DOT[i]<-NA
  }
}

for(i in 1:length(cvp$EID)){
  if (cvp$CFP_Vanc_DOT[i] == 0){
    cvp$CFP_Vanc_DOT[i]<-NA
  }
}

for(i in 1:length(cvp$EID)){
  ##gives a single Y/N variable for occurrence of hypotension
  n
  ifelse(cvp$MEAN_ARTERIAL_UNDER_60_FLG[i]=='Y' | cvp$HYPOTENSION_FLG[
i]=='Y' | ##this excludes SBP < 100 mmHg flag as this really isn't
defensible
        cvp$VASOPRESSORS_FLG[i]=='Y' | cvp$INOTROPES_FLG[i]=='Y',
        cvp$hypotension[i]<-'Y',cvp$hypotension[i]<-'N')
}

for(i in 1:length(cvp$EID)){
  ##Y/N for nephrotoxic drug exposure. Does not give a count.

  ifelse(cvp$ACYCLOVIR_FLG[i]=='Y' | cvp$AMINOGLYCOSIDES_FLG[i]=='Y' |
cvp$AMPHOTERICIN_B_FLG[i]=='Y' |

```



```

        cvp$ANGIOTENSIN_FLG[i]=='Y' | cvp$ANGIOTENSION_FLG[i]=='Y'
|cvp$COLISTIN_FLG[i]=='Y' |
        cvp$CYCLOSPORINE_FLG[i]=='Y' | cvp$FOSCARNET_FLG[i]=='Y' |
cvp$LOOP_DIURETICS_FLG[i]=='Y' |
        cvp$NON_STEROIDAL_ANTI_FLG[i]=='Y' | cvp$SULFONAMIDES_FLG[
i]=='Y' | cvp$TACROLIMUS_FLG[i]=='Y' |
        cvp$TENOFVIR_FLG[i]=='Y',cvp$nephrotoxic_drug[i]<-
"Y",cvp$nephrotoxic_drug[i]<-"N")
}

cvp<-
subset(cvp, is.na(cvp$RIFLE)==F)          ##cleaning up data, for
some reason patients are added at some point and a bunch of NAs are
added

for (i in 1:length(cvp$EID)){              ##Counts all nephr
otoxic drug exposure, dehydration, and dialysis flags
  n<-
  0                                          ##Ignores INTRAV_AGENTS
  _FLG because this is Y for all
  for (y in c(20:21, 23:30, 32:35)){
    if (cvp[i,y]=='Y'){
      n<-n+1
    }
  }
  cvp$rf_num[i] <- n
}

for (i in 1:length(cvp$EID)){              ##creates new vari
able that includes hypotension as a risk factor, avoids double count
ing
  if (cvp$hypotension[i]=='Y'){            ##multiple hypoten
sion exposures
    cvp$total_rf[i]<-cvp$rf_num[i]+1
  }
  else{
    cvp$total_rf[i]<-cvp$rf_num[i]
  }
}

for (i in 1:length(cvp$EID)){              ##groups # of risk
factors, 0-3, and 4+, coded as numerical value for math
  if (cvp$total_rf[i]==0){
    cvp$rf_group[i]<-0
  }
  if (cvp$total_rf[i]==1){
    cvp$rf_group[i]<-1
  }
  if (cvp$total_rf[i]==2){

```

```

    cvp$rf_group[i]<-2
  }
  if (cvp$total_rf[i]==3){
    cvp$rf_group[i]<-3
  }
  if (cvp$total_rf[i]>=4){
    cvp$rf_group[i]<-4
  }
}

for(i in 1:length(cvp$EID)){
  ##creates Y/N mortality variable
  if (cvp$DISCHRG_DES[i] == 'DEATH <=48 HRS' | cvp$DISCHRG_DES[i] == '
DEATH > 48 HRS' |
      cvp$DISCHRG_DES[i] == 'HOSPICE HOME' | cvp$DISCHRG_DES[i] == '
HOSPICE TO MED FAC'){
    cvp$mortality[i]<-'Y'
  }
  else{
    cvp$mortality[i]<-'N'
  }
}

source('f:/Jessica data/Test/dreg.R')          ##loads dreg script
  which finds the PTZ regimen; output = dreg_list
source('f:/Jessica data/Test/dreg2_cfp.R')     ##loads dreg2 scrip
t which finds the Cefepime regimen; output = dreg2_list

pv<-
subset(cvp, cvp$group=='PV')                    ##creates i
ntermediate subset to recreate the pmeds set
pmeds<-subset(cvpmeds, cvpmeds$Encounter.ID %in% pv$EID)
pmeds<-subset(pmeds, pmeds$drug=='PTZ')
dreg(pmeds)                                     ##calculates the PT
Z regimen based on max number of doses per day, if >=4 freq=Q6h, if
<= 3 freq =q8h
pdf<-ldply(dreg_list)                           ##list--
> dataframe
pdf2<-
pdf[pdf$V2==1,]                                ## finding patients who o
nly received 1 dose of PTZ per day,
cvp<-
subset(cvp, !(cvp$EID %in% pdf2$V1))           ##excluding above patien
ts
pdf3<-
subset(pdf, !(pdf$V1 %in% pdf2$V1))            ##subset of included pati
ents
names(pdf3)[names(pdf3)=='V1']<-
'EID'                                           ##renaming variables
names(pdf3)[names(pdf3)=='V2']<-'NUMBER'

```

```

names(pdf3)[names(pdf3)=='V3']<- 'ptz_dose'
names(pdf3)[names(pdf3)=='V4']<- 'ptz_freq'
cvp<-
merge(cvp, pdf3, by='EID', all=T)          ##combining datasets
cvp$ptz_reg<-
paste(cvp$ptz_dose, cvp$ptz_freq)  ##creating ptz_reg (regimen) variable for analysis and graphing

cv<-
subset(cvp, cvp$group=='CV')          ##same step as above except for cefepime
ps as above except for cefepime
cmeds<-subset(cvpmeds, cvpmeds$Encounter.ID %in% cv$EID)
cmeds<-subset(cmeds, cmeds$drug=="Cefepime")
dreg2(cmeds)
cdf<-
ldply(dreg2_list)                    ##Don't check for patients only receiving 1 dose per day as q24h is a valid regimen for cefepime
names(cdf)[names(cdf)=='V1']<- "EID"
names(cdf)[names(cdf)=='V2']<- "NUMBER"
names(cdf)[names(cdf)=='V3']<- "cfp_dose"
names(cdf)[names(cdf)=='V4']<- "cfp_freq"
cvp<-
merge(cvp, cdf, by="EID", all=T)      ##combining datasets
cvp$cfp_reg<-
paste(cvp$cfp_dose, cvp$cfp_freq)  ##cfp_reg variable created

cvp$NUMBER.x<-
NULL                                ##NUMBER.x and .y are created from the previous mergers, they are not needed anymore
cvp$NUMBER.y<-NULL

for (i in 1:length(cvp$EID)){        ##NA's induced by mergers, then pasted together(NA NA) from regimen variable creation. Setting to NA.
  if(cvp$ptz_reg[i]=='NA NA'){
    cvp$ptz_reg[i]<-NA
  }
  if(cvp$cfp_reg[i]=='NA NA'){
    cvp$cfp_reg[i]<-NA
  }
}

library(MatchIt)                    ##load the MatchIt package to perform matching
library(dplyr)                       ##load dplyr package for access to the 'select' function to create a subset

```

```

cvp$TOTAL_CHARLSON_SCORE<-
as.numeric(cvp$TOTAL_CHARLSON_SCORE) ##Set charlson score to numeri
c value to match on

for(i in 1:length(cvp$EID)){                                ##converting binary
  responses to 0/1 to match on.
  if(cvp$GENDER[i]=='MALE'){
    cvp$male[i]<-1
  }
  else{
    cvp$male[i]<-0
  }
}

for(i in 1:length(cvp$EID)){
  if(cvp$group[i]=='CV'){
    cvp$group_num[i]<-1
  }
  else{
    cvp$group_num[i]<-0
  }
}

for(i in 1:length(cvp$EID)){
  if(cvp$hypotension[i]=='Y'){
    cvp$hypotension_num[i]<-1
  }
  else{
    cvp$hypotension_num[i]<-0
  }
}

```

Matching

```

mdf<-
select(cvp, EID, group_num, AGE, TOTAL_CHARLSON_SCORE,
##subsets variables to match on, since matchit function doesn't
      Combo_DOT,hypotension_num,baseline_crcl, male, rf_group)
      ##like NAs in the data even if not in the matching variables li
ke in this case

m.out<-
matchit(group_num~AGE+rf_group+Combo_DOT+TOTAL_CHARLSON_SCORE+ ##
running the match on the mdf subset, using nearest neighbor method

```

```

        hypotension_num+baseline_crcl+male, data=mdf,
        ##ratio 3:1
        method='nearest',exact=c('male','hypotension_num','rf
_group'), ratio=3)

mat_data<-
match.data(m.out)                                ##setting up a dat
aframe with the matched variables, this contains distances and weigh
ts
cvp_matched<-
subset(cvp, cvp$EID %in% mat_data$EID)           ##Getting our final 3
:1 matched dataset.

assign("cvp",value=cvp,pos=globalenv())
assign("m.out",value=m.out,pos=globalenv())
assign("cvp_matched",value=cvp_matched,pos=globalenv())
}

library(stargazer)
library(sjPlot)
cvp_matched$first_vanc_trough<-
as.numeric(cvp_matched$first_vanc_trough)
cvp_matched$max_vanc_trough<-
as.numeric(cvp_matched$max_vanc_trough)
cvp_matched$percent_decrease<-cvp_matched$percent_change
for( i in 1:length(cvp_matched$EID)){
  if(cvp_matched$percent_decrease[i]==0){
    cvp_matched$percent_decrease[i]<-NA
  }
}

stargazer(cvp_matched[cvp_matched$group=='PV'],,
          type='text',title='Piperacillin/Tazobactam plus vancomycin
',
          digits=1, out='pv matched descriptive stats.txt')
stargazer(cvp_matched[cvp_matched$group=='CV'],,
          type='text',title='Cefepime plus vancomycin',
          digits=1, out='cv matched descriptive stats.txt')
stargazer(cvp[cvp$group=='PV'],,
          type='text',title='Piperacillin/Tazobactam plus vancomycin
',
          digits=1, out='pv unmatched descriptive stats.txt')
stargazer(cvp[cvp$group=='CV'],,
          type='text',title='Cefepime plus vancomycin',
          digits=1, out='cv unmatched descriptive stats.txt')

matvanc<-
subset(cvp_matched, cvp_matched$first_vanc_class!='No levels')

```

```

risk<-table(cvp_matched$RIFLE=='RISK', cvp_matched$group)
injury<-table(cvp_matched$RIFLE=='INJURY', cvp_matched$group)
fail<-table(cvp_matched$RIFLE=='Failure', cvp_matched$group)
any_aki<-table(cvp_matched$RIFLE!='No injury', cvp_matched$group)
fsub<-
table(matvanc$first_vanc_class=='subtherapeutic', matvanc$group)
flow<-
table(matvanc$first_vanc_class=='low_therapeutic', matvanc$group)
fhigh<-
table(matvanc$first_vanc_class=='high_therapeutic', matvanc$group)
fsup<-
table(matvanc$first_vanc_class=='supratherapeutic', matvanc$group)
ftx<-table(matvanc$first_vanc_class == 'low_therapeutic' |
           matvanc$first_vanc_class=='high_therapeutic', matvanc$g
roup)
fv30<-table(matvanc$first_vanc_trough>30,matvanc$group)

matvanc<-
subset(cvp_matched, cvp_matched$max_vanc_class!='No levels')

msub<-
table(matvanc$max_vanc_class=='subtherapeutic', matvanc$group)
mlow<-
table(matvanc$max_vanc_class=='low_therapeutic', matvanc$group)
mhigh<-
table(matvanc$max_vanc_class=='high_therapeutic', matvanc$group)
msup<-
table(matvanc$max_vanc_class=='supratherapeutic', matvanc$group)
mtx<-table(matvanc$max_vanc_class=='low_therapeutic' |
           matvanc$max_vanc_class=='high_therapeutic', matvanc$gro
up)
mv30<-table(matvanc$max_vanc_trough>30,matvanc$group)

attach(cvp_matched)

```

Data table generation

```

sink('Outcomes and baseline characteristics output.txt')
print('***** T-test results*****')
lapply(cvp_matched[,c('AGE', 'TOTAL_CHARLSON_SCORE', 'LENGTH_OF_STAY_N
UM',
                     'baseline_scr', 'baseline_crcl', 'min_crcl', 'pe
rcent_change', 'percent_decrease',
                     'avg_daily_vanc_dose', 'first_vanc_trough', 'ma
x_vanc_trough',
                     'Total_DOT', 'Vanc_DOT', 'Combo_DOT', 'rf_num'
, 'total_rf',

```

```

                                'rf_group','male']], function(x) t.test(x~cvp
_matched$group))
t.test(CFP_DOT[group=='CV'], PTZ_DOT[group=='PV'])

print('')
print('')
print('')
print('*****Wilcoxon Rank Sum tests for nonparametric analysis**
*****')
lapply(cvp_matched[,c('AGE','TOTAL_CHARLSON_SCORE','LENGTH_OF_STAY_N
UM',
                                'baseline_scr','baseline_crcl','percent_change
','percent_decrease',
                                'avg_daily_vanc_dose','first_vanc_trough','max
_vanc_trough',
                                'Total_DOT','Vanc_DOT','Combo_DOT','rf_num','
total_rf',
                                'rf_group','male']], function(x) wilcox.test(x
~cvp_matched$group))
wilcox.test(CFP_DOT[group=='CV'], PTZ_DOT[group=='PV'])

print('')
print('')
print('')
print('*****Piperacillin/Tazobactam and vancomycin summary result
s*****')
lapply(cvp_matched[,c('AGE','TOTAL_CHARLSON_SCORE','LENGTH_OF_STAY_N
UM',
                                'baseline_scr','baseline_crcl','percent_change
','percent_decrease',
                                'avg_daily_vanc_dose','first_vanc_trough','max
_vanc_trough',
                                'Total_DOT','Vanc_DOT','Combo_DOT','rf_num','
total_rf',
                                'rf_group','male']], function(x) summary(x[grou
up=='PV']))

print('')
print('')
print('')
print('*****Cefepime and vancomycin summary results*****')
lapply(cvp_matched[,c('AGE','TOTAL_CHARLSON_SCORE','LENGTH_OF_STAY_N
UM',
                                'baseline_scr','baseline_crcl','percent_change
','percent_decrease',
                                'avg_daily_vanc_dose','first_vanc_trough','max
_vanc_trough',
                                'Total_DOT','Vanc_DOT','Combo_DOT','rf_num','
total_rf',

```

```

                                'rf_group','male']], function(x) summary(x[gro
up=='CV']))
print('')
print('')
print('')
print('*****Primary outcomes*****')
chisq.test(risk)
risk
prop.table(risk,2)*100
chisq.test(injury)
injury
prop.table(injury,2)*100
chisq.test(fail)
fail
prop.table(fail,2)*100
chisq.test(any_aki)
any_aki
prop.table(any_aki,2)*100

print('')
print('')
print('')
print('*****Baseline matched cohort characteristics*****')
chisq.test(table(GENDER, group))
table(GENDER, group)
prop.table(table(GENDER, group),2)*100

chisq.test(table(mortality, group))
table(mortality, group)
prop.table(table(mortality, group),2)*100

chisq.test(table(DIALYSIS_FLG,group))
table(DIALYSIS_FLG,group)
prop.table(table(DIALYSIS_FLG,group),2)*100

chisq.test(table(DEHYDRATION_FLG, group))
table(DEHYDRATION_FLG, group)
prop.table(table(DEHYDRATION_FLG, group),2)*100

chisq.test(table(hypotension,group))
table(hypotension,group)
prop.table(table(hypotension,group),2)*100

chisq.test(table(nephrotoxic_drug,group))
table(nephrotoxic_drug,group)
prop.table(table(nephrotoxic_drug,group),2)*100

```



```

chisq.test(table(ACYCLOVIR_FLG, group))
table(ACYCLOVIR_FLG, group)
prop.table(table(ACYCLOVIR_FLG, group),2)*100

chisq.test(table(ANGIOTENSIN_FLG, group))
table(ANGIOTENSIN_FLG, group)
prop.table(table(ANGIOTENSIN_FLG, group),2)*100

chisq.test(table(ANGIOTENSION_FLG, group))
table(ANGIOTENSION_FLG, group)
prop.table(table(ANGIOTENSION_FLG, group),2)*100

chisq.test(table(AMINOGLYCOSIDES_FLG, group))
table(AMINOGLYCOSIDES_FLG, group)
prop.table(table(AMINOGLYCOSIDES_FLG, group),2)*100

chisq.test(table(AMPHOTERICIN_B_FLG, group))
table(AMPHOTERICIN_B_FLG, group)
prop.table(table(AMPHOTERICIN_B_FLG, group),2)*100

chisq.test(table(CYCLOSPORINE_FLG, group))
fisher.test(table(CYCLOSPORINE_FLG, group))
table(CYCLOSPORINE_FLG, group)
prop.table(table(CYCLOSPORINE_FLG, group),2)*100

chisq.test(table(FOSCARNET_FLG,group))
fisher.test(table(FOSCARNET_FLG,group))
table(FOSCARNET_FLG,group)
prop.table(table(FOSCARNET_FLG,group),2)*100

chisq.test(table(LOOP_DIURETICS_FLG,group))
table(LOOP_DIURETICS_FLG,group)
prop.table(table(LOOP_DIURETICS_FLG,group),2)*100

chisq.test(table(NON_STEROIDAL_ANTI_FLG, group))
table(NON_STEROIDAL_ANTI_FLG, group)
prop.table(table(NON_STEROIDAL_ANTI_FLG, group),2)*100

chisq.test(table(SULFONAMIDES_FLG, group))
table(SULFONAMIDES_FLG, group)
prop.table(table(SULFONAMIDES_FLG, group),2)*100

chisq.test(table(TACROLIMUS_FLG, group))
table(TACROLIMUS_FLG, group)
prop.table(table(TACROLIMUS_FLG, group),2)*100

chisq.test(table(TENOFOVIR_FLG,group))
fisher.test(table(TENOFOVIR_FLG,group))
table(TENOFOVIR_FLG,group)

```

```

prop.table(table(TENOFOVIR_FLG,group),2)*100

table(rf_group,group)
chisq.test(rf_group==0,group)
chisq.test(rf_group==1,group)
chisq.test(rf_group==2,group)
chisq.test(rf_group==3,group)
chisq.test(rf_group==4,group)

print('')
print('')
print('')
print('Vancomycin classifications - first vancomycin trough')
addmargins(table(cvp_matched$first_vanc_class, cvp_matched$group),1)

chisq.test(fsub)
fsub
prop.table(fsub,2)*100
chisq.test(flow)
flow
prop.table(flow,2)*100
chisq.test(fhigh)
fhigh
prop.table(fhigh,2)*100
chisq.test(fsup)
fsup
prop.table(fsup, 2)*100
chisq.test(ftx)
ftx
prop.table(ftx, 2)*100
chisq.test(fv30)
fv30
prop.table(fv30,2)*100

print('')
print('')
print('')
print('Vancomycin classifications - max vancomycin trough')
print('Table of maximum vanc troughs by group')
addmargins(table(cvp_matched$max_vanc_class, cvp_matched$group),1)

chisq.test(msub)
msub
prop.table(msub,2)*100
chisq.test(mlow)
mlow
prop.table(mlow, 2)*100

```

```

chisq.test(mhigh)
mhigh
prop.table(mhigh, 2)*100
chisq.test(msup)
msup
prop.table(msup,2)*100
chisq.test(mtx)
mtx
prop.table(mtx,2)*100
chisq.test(mv30)
mv30
prop.table(mv30,2)*100

chisq.test(table(avg_daily_vanc_dose<500, group))
table(avg_daily_vanc_dose<500, group)
prop.table(table(avg_daily_vanc_dose<500, group),2)*100

chisq.test(table(avg_daily_vanc_dose>=500 & avg_daily_vanc_dose<1000
, group))
table(avg_daily_vanc_dose>=500 & avg_daily_vanc_dose<1000, group)
prop.table(table(avg_daily_vanc_dose>=500 & avg_daily_vanc_dose<1000
, group),2)*100

chisq.test(table(avg_daily_vanc_dose>=1000 & avg_daily_vanc_dose<1500
, group))
table(avg_daily_vanc_dose>=1000 & avg_daily_vanc_dose<1500, group)
prop.table(table(avg_daily_vanc_dose>=1000 & avg_daily_vanc_dose<1500
, group),2)*100

chisq.test(table(avg_daily_vanc_dose>=1500 & avg_daily_vanc_dose<2000
, group))
table(avg_daily_vanc_dose>=1500 & avg_daily_vanc_dose<2000, group)
prop.table(table(avg_daily_vanc_dose>=1500 & avg_daily_vanc_dose<2000
, group),2)*100

chisq.test(table(avg_daily_vanc_dose>=2000, group))
table(avg_daily_vanc_dose>=2000, group)
prop.table(table(avg_daily_vanc_dose>=2000, group),2)*100

chisq.test(table(avg_daily_vanc_dose>=3000, group))
table(avg_daily_vanc_dose>=3000, group)
prop.table(table(avg_daily_vanc_dose>=3000, group),2)*100

chisq.test(table(avg_daily_vanc_dose>=4000, group))
table(avg_daily_vanc_dose>=4000, group)
prop.table(table(avg_daily_vanc_dose>=4000, group),2)*100

```

```

sink()

sink('AKI analysis output.txt')
print('*****AKI t test analysis*****')
lapply(cvp_matched[,c('AGE', 'TOTAL_CHARLSON_SCORE', 'LENGTH_OF_STAY_N
UM',
                    'baseline_scr', 'baseline_crcl', 'percent_change
', 'percent_decrease',
                    'avg_daily_vanc_dose', 'first_vanc_trough', 'max
_vanc_trough',
                    'Total_DOT', 'Vanc_DOT', 'Combo_DOT', 'PTZ_DOT',
'CFP_DOT', 'CFP_Vanc_DOT',
                    'PTZ_Vanc_DOT', 'rf_num', 'total_rf', 'rf_group'
, 'male')]],
      function(x) t.test(x~cvp_matched$AKI))
print('')
print('')
print('')
print('*****AKI Wilcoxon Rank Sum tests for nonparametric analys
is*****')
lapply(cvp_matched[,c('AGE', 'TOTAL_CHARLSON_SCORE', 'LENGTH_OF_STAY_N
UM',
                    'baseline_scr', 'baseline_crcl', 'percent_change
', 'percent_decrease',
                    'avg_daily_vanc_dose', 'first_vanc_trough', 'max
_vanc_trough',
                    'Total_DOT', 'Vanc_DOT', 'Combo_DOT', 'PTZ_DOT',
'CFP_DOT', 'CFP_Vanc_DOT',
                    'PTZ_Vanc_DOT', 'rf_num', 'total_rf', 'rf_group'
, 'male')]],
      function(x) wilcox.test(x~cvp_matched$AKI))

print('')
print('')
print('')
print('*****AKI group summary results*****')
lapply(cvp_matched[,c('AGE', 'TOTAL_CHARLSON_SCORE', 'LENGTH_OF_STAY_N
UM',
                    'baseline_scr', 'baseline_crcl', 'percent_change
', 'percent_decrease',
                    'avg_daily_vanc_dose', 'first_vanc_trough', 'max
_vanc_trough',
                    'Total_DOT', 'Vanc_DOT', 'Combo_DOT', 'PTZ_DOT',
'CFP_DOT', 'CFP_Vanc_DOT',
                    'PTZ_Vanc_DOT', 'rf_num', 'total_rf', 'rf_group'
, 'male')]],
      function(x) summary(x[AKI=='AKI']))

```

```

print('')
print('')
print('')
print('*****No AKI summary results*****')
lapply(cvp_matched[,c('AGE', 'TOTAL_CHARLSON_SCORE', 'LENGTH_OF_STAY_NUM',
                      'baseline_scr', 'baseline_crcl', 'percent_change',
                      'percent_decrease',
                      'avg_daily_vanc_dose', 'first_vanc_trough', 'max_vanc_trough',
                      'Total_DOT', 'Vanc_DOT', 'Combo_DOT', 'PTZ_DOT',
                      'CFP_DOT', 'CFP_Vanc_DOT',
                      'PTZ_Vanc_DOT', 'rf_num', 'total_rf', 'rf_group',
                      'male')],
       function(x) summary(x[AKI=='No AKI']))

print('')
print('')
print('')
print('*****AKI by nephrotoxin exposure*****')
addmargins(table(cvp_matched$RIFLE, cvp_matched$nephrotoxic_drug),1)
prop.table(table(cvp_matched$RIFLE, cvp_matched$nephrotoxic_drug),2)
*100
chisq.test(table(cvp_matched$RIFLE=='RISK', cvp_matched$nephrotoxic_drug))
chisq.test(table(cvp_matched$RIFLE=='INJURY', cvp_matched$nephrotoxic_drug))
chisq.test(table(cvp_matched$RIFLE=='Failure', cvp_matched$nephrotoxic_drug))
chisq.test(table(cvp_matched$RIFLE!='No injury', cvp_matched$nephrotoxic_drug))

print('')
print('')
print('')
print('*****AKI by nephrotoxin exposure*****')
addmargins(table(cvp_matched$RIFLE, cvp_matched$hypotension),1)
prop.table(table(cvp_matched$RIFLE, cvp_matched$hypotension),2)*100

chisq.test(table(cvp_matched$RIFLE=='RISK', cvp_matched$hypotension))
chisq.test(table(cvp_matched$RIFLE=='INJURY', cvp_matched$hypotension))
chisq.test(table(cvp_matched$RIFLE=='Failure', cvp_matched$hypotension))
chisq.test(table(cvp_matched$RIFLE!='No injury', cvp_matched$hypotension))

```

```

sink()

p3<-
subset(cvp_matched, cvp_matched$ptz_reg == '4.5 Q6H' | cvp_matched$ptz_
reg=='3.375 Q6H')
detach(cvp_matched)
attach(p3)

sink('PTZ regimen results.txt')

addmargins(table(RIFLE, ptz_reg))
prop.table(table(RIFLE, ptz_reg),2)*100
chisq.test(table(RIFLE=='RISK',ptz_reg))
chisq.test(table(RIFLE=='INJURY',ptz_reg))
chisq.test(table(RIFLE=='Failure',ptz_reg))
chisq.test(table(RIFLE!='No injury',ptz_reg))

sink()

write.table(cvp, row.names=F, 'AKI_dataset_FINAL.txt', sep=',')
write.table(cvp_matched, row.names=F, 'AKI_matched_dataset_FINAL.txt
', sep=',')
sink('matching diagnostics.txt')
m.out
summary(m.out)
sink()

```

Appendix B: Chapter 3 code

Data wrangling

```
library(plyr)
library(dplyr)
library(data.table)
dat<-
read.csv('//file2/crutter/UKHC - Cotner, Sarah - 2016/Cotner/cotner_
drugs.csv', sep=',', colClasses='character')
dem<-
fread('//file2/crutter/UKHC - Cotner, Sarah - 2016/Cotner/cotner_dem
o.csv',
      sep=',', colClasses='character')
dx<-
fread('//file2/crutter/UKHC - Cotner, Sarah - 2016/Cotner/COTNER_DX2
016-02-17 11-41-11.csv',
      sep=',', colClasses='character')
ht<-
fread('//file2/crutter/UKHC - Cotner, Sarah - 2016/Cotner/COTNER_HT_
WT2016-02-17 11-42-07.csv', sep=',',
      colClasses='character')

merid<-
unique(dat$ENCNTR_ID[grepl('meropenem', dat$NAME, ignore.case = T)])

pipid<-
unique(dat$ENCNTR_ID[grepl('piperacillin', dat$NAME, ignore.case = T
)])
cfpid<-
unique(dat$ENCNTR_ID[grepl('cefepime', dat$NAME, ignore.case = T)])

cfpmem<-intersect(cfpid, merid)
cfppip<-intersect(cfpid, pipid)
cfpmempip<-intersect(cfpmem, cfppip)
pipmem<-intersect(pipid, merid)

test<-
unique(dat$ENCNTR_ID[dat$ENCNTR_ID %in% merid | dat$ENCNTR_ID %in% p
ipid | dat$ENCNTR_ID %in% cfpid])
df<-data.frame(EID = test, group = NA)

df$group[df$EID %in% cfpid]<- 'C'
df$group[df$EID %in% pipid]<- 'P'
df$group[df$EID %in% merid]<- 'M'
df$group[df$EID %in% cfpmem]<- 'CM'
```

```

df$group[df$EID %in% cfppip]<- 'CP'
df$group[df$EID %in% pipmem]<- 'MP'
df$group[df$EID %in% cfmempip]<- 'CMP'

m_final=as.character(df$EID[df$group=='M'])
p_final=as.character(df$EID[df$group=='P'])
rm(asid, cfpid, pipid, merid, aspip, ascfp, asmem, cfpmem, cfppip, p
ipmem, aspipmem, ascfpmem, aspipcfp, aspipcfpmem, cfmempip, test)
#####
#####
##                               Demographics clean up
##                               ##
#####
#####
dem<-dem[dem$ENCNTR_ID %in% m_final | dem$ENCNTR_ID %in% p_final,]
dem$drug[dem$ENCNTR_ID %in% m_final]<- 'MEM'
dem$drug[dem$ENCNTR_ID %in% p_final]<- 'PTZ'
dem<-dem[!duplicated(dem$ENCNTR_ID),]

dem$ad_date<-sapply(strsplit(dem$ADMT_DT, ' '), '[',1)
dem$ad_date<-as.Date(dem$ad_date, format='%d-%b-%y')

dem<-dem[dplyr::between(dem$ad_date,
                        left = as.Date('2006-07-01'),
                        right = as.Date('2015-09-30')
                        #incbounds = T
),]
dem$COMORBIDITY_SCORE<-as.numeric(dem$COMORBIDITY_SCORE)
dem$COMORBIDITY_SCORE[is.na(dem$COMORBIDITY_SCORE)]<-0
dem$AGE<-as.numeric(dem$AGE)
dem<-dem[dem$AGE >= 18,]
dem$age_group[dem$AGE<45]<- '18-44'
dem$age_group[dem$AGE>=45 & dem$AGE <65]<- '45-64'
dem$age_group[dem$AGE>=65 & dem$AGE <80]<- '65-79'
dem$age_group[dem$AGE>=80]<- '80+'

dem$LENGTH_OF_STAY_NUM<-as.numeric(dem$LENGTH_OF_STAY_NUM)

pregeid<-
unique(dx$FULL_ENC_NTR_ID[grepl('v22',dx$DX_CD, ignore.case = T)])
dem<-dem[!(dem$ENCNTR_ID %in% pregeid),]

ckdeid<-
unique(dx$FULL_ENC_NTR_ID[grepl('585\\. [12349]', dx$DX_CD, ignore.cas
e = T)])
dem<-dem[!(dem$ENCNTR_ID %in% ckdeid),]

```



```

cf<-
unique(dx$FULL_ENC_NTR_ID[grepl('277\\.', dx$DX_CD, ignore.case = T)]
)
dem$CF[dem$ENC_NTR_ID %in% cf]<-1
dem$CF[is.na(dem$CF)]<-0

htn<-
unique(dx$FULL_ENC_NTR_ID[grepl('401\\.', dx$DX_CD, ignore.case = T)]
)
dem$HTN[dem$ENC_NTR_ID %in% htn]<-1
dem$HTN[is.na(dem$HTN)]<-0

dm<-
unique(dx$FULL_ENC_NTR_ID[grepl('250\\.', dx$DX_CD, ignore.case = T)]
)
dem$dm[dem$ENC_NTR_ID %in% dm]<-1
dem$dm[is.na(dem$dm)]<-0

hf<-
unique(dx$FULL_ENC_NTR_ID[grepl('428\\.', dx$DX_CD, ignore.case = T)]
)
dem$hf[dem$ENC_NTR_ID %in% hf]<-1
dem$hf[is.na(dem$hf)]<-0

ht<-ht[ht$ENC_NTR_ID %in% dem$ENC_NTR_ID,]
ht$INIT_WT<-as.numeric(ht$INIT_WT)
ht$HT<-as.numeric(ht$HT)
ht$WT<-as.numeric(ht$WT)
ht$INIT_WT[is.na(ht$INIT_WT)]<-ht$WT[is.na(ht$INIT_WT)]
ht2<-select(ht, ENC_NTR_ID, INIT_WT, HT)

dem<-merge(dem, ht2, by='ENC_NTR_ID', all=T)
dem$INIT_WT[dem$INIT_WT==0]<-NA
dem$HT[dem$HT==0]<-NA

wtcut<-mean(dem$INIT_WT, na.rm=T)+4*sd(dem$INIT_WT, na.rm=T)
dem<-dem[dem$INIT_WT<=wtcut | is.na(dem$INIT_WT),]
htcut<-mean(dem$HT, na.rm=T)+4*sd(dem$HT, na.rm=T)
dem<-dem[dem$HT<=htcut | is.na(dem$HT),]
dem<-dem[dem$HT>27 | is.na(dem$HT),]

dem$BMI<-dem$INIT_WT/((dem$HT/100)**2)
rm(ckdeid, pregeid, ht, ht2, wtcut, htcut, dm, hf, htn,a_final, p_fi
nal, cf, df, crcl_cut)
#####
#####
##
Medications clean up
##

```

```
#####
#####
meds<-dat
rm(dat)
meds<-meds[meds$ENCNTR_ID %in% dem$ENCNTR_ID,]
abx<-
meds[grepl('meropenem', meds$NAME, ignore.case = T) | grepl('piperac
illin', meds$NAME, ignore.case = T),]
abx$admin_date<-
sapply(strsplit(abx$PERFRMD_FROM_DT_TM, ' '), '[' ,1)
abx$admin_date<-as.Date(abx$admin_date, format = '%d-%b-%y')

dem$tx_index<-NA
dem$tx_end<-NA
dem$DOT<-NA

abx2<-select(abx, ENCNTR_ID, admin_date)
abx2<-unique(abx2)

for(i in 1:nrow(dem)){                                ##~1.2
  hrs to complete
  dem$tx_index[i] = min(abx2$admin_date[abx2$ENCNTR_ID == dem$ENCNTR
_ID[i]])
  dem$tx_end[i] = max(abx2$admin_date[abx2$ENCNTR_ID == dem$ENCNTR_I
D[i]])
  dem$DOT[i]<-
length(unique(abx2$admin_date[abx2$ENCNTR_ID == dem$ENCNTR_ID[i]]))
}
dem$tx_index<-as.Date(dem$tx_index, origin='1970-01-01')
dem$tx_end<-as.Date(dem$tx_end, origin='1970-01-01')

dem<-dem[dem$DOT>=2,]

dem$caucasian[dem$RACE_CD_DES=='WHITE']<-1
dem$caucasian[is.na(dem$caucasian)]<-0

dem$ad_year<-sapply(strsplit(as.character(dem$ad_date), '-
'), '[' ,1)
dem<-dem[dem$GENDR_CD_DES !='UNKNOWN',]
#####
#####
##                                labs                                ##
#####
#####
labs<-
fread('///file2/crutter/UKHC - Cotner, Sarah - 2016/Cotner/labs.txt',
sep='\t',header=T, colClasses='character')
```

```

labs<-labs[labs$ENCNTR_ID %in% dem$ENCNTR_ID]
scr<-labs[labs$ITM_NM == 'Creatinine Level',]
scr$date<-as.POSIXct(scr$ENTRD_DT_TM, format='%d-%b-%y %H:%M:%S')
scr$VAL_NUM<-as.numeric(scr$VAL_NUM)
scr<-scr[!is.na(scr$VAL_NUM),]

dem<-dem[dem$ENCNTR_ID %in% scr$ENCNTR_ID,]
for(i in 1:nrow(dem)){
  x<- scr[scr$ENCNTR_ID == dem$ENCNTR_ID[i],]
  dem$baseline_scr[i]<-x$VAL_NUM[x$date==min(x$date)]
  dem$baseline_scr_date[i]<-min(x$date)}

dem$baseline_crcl<-(140-dem$AGE)/dem$baseline_scr
dem$baseline_crcl[dem$GENDR_CD_DES=='FEMALE']<-
dem$baseline_crcl[dem$GENDR_CD_DES=='FEMALE']*0.85

dem<-dem[!is.na(dem$baseline_scr),]
dem<-dem[dem$baseline_crcl>=30,]
crclcut<-
mean(dem$baseline_crcl, na.rm = T)+4*sd(dem$baseline_crcl)
dem<-dem[dem$baseline_crcl<=crclcut,]

scr$date2<-sapply(strsplit(as.character(scr$date), ' '), '[' ,1)
scr$date2<-as.Date(scr$date2)

for(i in 1:nrow(dem)){
  x<- scr[scr$ENCNTR_ID == dem$ENCNTR_ID[i] & scr$date2 >= dem$tx_in
dex[i]+2 & scr$date2<dem$tx_end[i]+7,]
  dem$max_scr[i]<-max(x$VAL_NUM)[1]
  dem$max_scr_date[i]<-x$date2[x$VAL_NUM==max(x$VAL_NUM)][1]}

dem$min_crcl<-(140-dem$AGE)/dem$max_scr
dem$min_crcl[dem$GENDR_CD_DES=='FEMALE']<-
dem$min_crcl[dem$GENDR_CD_DES=='FEMALE']*0.85
dem$percent_change<-(dem$min_crcl/dem$baseline_crcl-1)*100
dem<-dem[!is.infinite(dem$max_scr),]

dem$RIFLE[dem$percent_change <= -25 & dem$percent_change >-50]<-
'risk'
dem$RIFLE[dem$percent_change <= -50 & dem$percent_change >-75]<-
'injury'
dem$RIFLE[dem$percent_change <= -75 | dem$max_scr>4]<- 'failure'

dem$aki[is.na(dem$RIFLE)]<-0
dem$aki[!is.na(dem$RIFLE)]<-1

```

```

dem$baseline_crcl_cat[dem$baseline_crcl <60]<-1
dem$baseline_crcl_cat[dem$baseline_crcl >=60 & dem$baseline_crcl<90]
<-2
dem$baseline_crcl_cat[dem$baseline_crcl >=90]<-3
#####
#####
##                               Nephrotoxin info                               ##
#####
#####
library(stringr)
neph<-
read.csv('//file2/crutter/UKHC - Cotner, Sarah - 2016/Cotner/COTNER_
NEPHROTOXIN.csv', colClasses='character')

# vid<-
unique(meds$ENCNTR_ID[grepl('vancomycin', meds$NAME, ignore.case = T
)])
# dem<- dem[!(dem$ENCNTR_ID %in% vid),]

vanc<-meds[grepl('vanco', meds$NAME, ignore.case = T),]
vanc<-vanc[grepl('v', vanc$TASK_ROUT_CD, ignore.case = T),]
# vanc$NAME<-gsub('zzz','',vanc$NAME)
# vanc$NAME<-gsub('inj','',vanc$NAME, ignore.case = T)
# vanc$NAME<-gsub('\\.','',vanc$NAME)
# vanc$NAME<-gsub('-', '',vanc$NAME)
# vanc$NAME<-gsub('\\(pediatric\\)','',vanc$NAME, ignore.case = T)
# vanc$NAME<-str_trim(vanc$NAME)
vanc$date<-sapply(strsplit(vanc$PERFRMD_FROM_DT_TM, ' '), '[',1)
vanc$date<-as.Date(vanc$date, format = '%d-%b-%y')

ag<-
meds[grepl('aminogly', meds$THERPUTC_CATGRY, ignore.case = T),]
ag<-ag[!grepl('inhal', ag$NAME, ignore.case = T),]
ag<-ag[!grepl('irrigat', ag$NAME, ignore.case = T),]
ag<-ag[!grepl('neomycin', ag$NAME, ignore.case = T),]
# ag$NAME<-gsub('zzz','',ag$NAME)
# ag$NAME<-gsub('inj','',ag$NAME, ignore.case = T)
# ag$NAME<-gsub('\\.','',ag$NAME)
# ag$NAME<-gsub('-', '',ag$NAME)
# ag$NAME<-gsub('\\(pediatric\\)','',ag$NAME, ignore.case = T)
# ag$NAME<-str_trim(ag$NAME)
ag$date<-sapply(strsplit(ag$PERFRMD_FROM_DT_TM, ' '), '[',1)
ag$date<-as.Date(ag$date, format = '%d-%b-%y')

amphb<-meds[grepl('amphote', meds$NAME, ignore.case = T),]
amphb<-amphb[!grepl('inhal', amphb$NAME, ignore.case = T),]
amphb<-amphb[!grepl('irrigat', amphb$NAME, ignore.case = T),]

```

```

# amphb$NAME<-gsub('zzz','',amphb$NAME)
# amphb$NAME<-gsub('inj','',amphb$NAME, ignore.case = T)
# amphb$NAME<-gsub('\.\.','',amphb$NAME)
# amphb$NAME<-gsub('-','',amphb$NAME)
# amphb$NAME<-
gsub('\(pediatric\)','',amphb$NAME, ignore.case = T)
# amphb$NAME<-str_trim(amphb$NAME)
amphb$date<-sapply(strsplit(amphb$PERFRMD_FROM_DT_TM, ' '), '[' ,1)
amphb$date<-as.Date(amphb$date, format = '%d-%b-%y')

cont<-neph[neph$NAME == '(ADM Override)',]
cont<-
cont[grepl('gado', cont$TASK_NM, ignore.case = T) | grepl('iodix', c
ont$TASK_NM, ignore.case = T)|
      grepl('iohex', cont$TASK_NM, ignore.case = T)| grepl('i
othal', cont$TASK_NM, ignore.case = T),]
cont<-cont[!grepl('oral', cont$TASK_NM, ignore.case = T),]
cont$date<-sapply(strsplit(cont$PERFRMD_FROM_DT_TM, ' '), '[' ,1)
cont$date<-as.Date(cont$date)#, format = '%d-%b-%y')
cont<-cont[!is.na(cont$date),]

nsaids<-
meds[grepl('ibuprofen', meds$NAME, ignore.case=T)|grepl('naproxen',
meds$NAME, ignore.case=T)|
      grepl('indomethacin', meds$NAME, ignore.case=T)|grepl(
('ketorolac', meds$NAME, ignore.case=T)|
      grepl('meloxicam', meds$NAME, ignore.case=T)|grepl('c
elecoxib', meds$NAME, ignore.case=T)|
      grepl('diclofenac', meds$NAME, ignore.case=T)|grepl('
etodolac', meds$NAME, ignore.case=T)|
      grepl('nabumetone', meds$NAME, ignore.case=T)|grepl('
piroxicam', meds$NAME, ignore.case=T)|
      grepl('sulindac', meds$NAME, ignore.case=T),]
nsaids$date<-
sapply(strsplit(nsaids$PERFRMD_FROM_DT_TM, ' '), '[' ,1)
nsaids$date<-as.Date(nsaids$date, format = '%d-%b-%y')

#Need to follow up with Andrew
calc<-neph[neph$DRUG_KEY %in% c('d03752','d00079'),]
calc$date<-sapply(strsplit(calc$PERFRMD_FROM_DT_TM, ' '), '[' ,1)
calc$date<-as.Date(calc$date)#, format = '%d-%b-%y')
calc<-calc[!is.na(calc$date),]

loop<-
meds[grepl('furosemide', meds$NAME, ignore.case=T)|grepl('bumetanide
', meds$NAME, ignore.case=T)|
      grepl('torsemide', meds$NAME, ignore.case=T)|grepl('eth
acryn', meds$NAME, ignore.case=T),]
loop$date<-sapply(strsplit(loop$PERFRMD_FROM_DT_TM, ' '), '[' ,1)

```

```

loop$date<-as.Date(loop$date, format = '%d-%b-%y')

vaso<-
meds[grepl('norepinephrine', meds$NAME, ignore.case=T)|grepl('epinephrine', meds$NAME, ignore.case=T)|
      grepl('phenylephrine', meds$NAME, ignore.case=T)|grepl('vasopressin', meds$NAME, ignore.case=T)|
      grepl('dopamine', meds$NAME, ignore.case=T),]
vaso$date<-sapply(strsplit(vaso$PERFRMD_FROM_DT_TM, ' '), '[' ,1)
vaso$date<-as.Date(vaso$date, format = '%d-%b-%y')

iono<-
meds[grepl('Dobutamine', meds$NAME, ignore.case=T)|grepl('milrinone', meds$NAME, ignore.case=T),]
iono$date<-sapply(strsplit(iono$PERFRMD_FROM_DT_TM, ' '), '[' ,1)
iono$date<-as.Date(iono$date, format = '%d-%b-%y')

acei<-neph[grepl('pril', neph$NAME, ignore.case=T),]
acei$date<-sapply(strsplit(acei$PERFRMD_FROM_DT_TM, ' '), '[' ,1)
acei$date<-as.Date(acei$date)#, format = '%d-%b-%y')
acei<-acei[complete.cases(acei),]

# NEd to follow up with Andrew
arb<-
neph[neph$DRUG_KEY %in% c('d03821', 'd04322', 'd04113', 'd04222', 'd04364', 'd04801'),]
arb$date<-sapply(strsplit(arb$PERFRMD_FROM_DT_TM, ' '), '[' ,1)
arb$date<-as.Date(arb$date)#, format = '%m/%d/%Y')
arb<-arb[!is.na(arb$date),]

for(i in 1:nrow(dem)){
  if(!(dem$ENCNTR_ID [i] %in% vanc$ENCNTR_ID)){
    dem$vanc_exp[i]<-0
    next
  }
  else{
    x<-vanc[vanc$ENCNTR_ID == dem$ENCNTR_ID[i],]
    x<-x[dplyr::between(x = x$date, left = dem$tx_index[i]-1, right = dem$tx_end[i]),]
    if(dim(x)[1]>0){
      dem$vanc_exp[i]<-1
    }
    else{
      dem$vanc_exp[i]<-0
    }
  }
}

for(i in 1:nrow(dem)){

```

```

if(!(dem$ENCNTR_ID [i] %in% ag$ENCNTR_ID)){
  dem$aminoglycoside_exp[i]<-0
  next
}
else{
  x<-ag[ag$ENCNTR_ID == dem$ENCNTR_ID[i],]
  x<-x[dplyr::between(x = x$date, left = dem$tx_index[i]-
1, right = dem$tx_end[i]),]
  if(dim(x)[1]>0){
    dem$aminoglycoside_exp[i]<-1
  }
  else{
    dem$aminoglycoside_exp[i]<-0
  }
}
}

for(i in 1:nrow(dem)){
  if(!(dem$ENCNTR_ID [i] %in% amphb$ENCNTR_ID)){
    dem$amphb_exp[i]<-0
    next
  }
  else{
    x<-amphb[amphb$ENCNTR_ID == dem$ENCNTR_ID[i],]
    x<-x[dplyr::between(x = x$date, left = dem$tx_index[i]-
1, right = dem$tx_end[i]),]
    if(dim(x)[1]>0){
      dem$amphb_exp[i]<-1
    }
    else{
      dem$amphb_exp[i]<-0
    }
  }
}

for(i in 1:nrow(dem)){
  if(!(dem$ENCNTR_ID [i] %in% cont$ENCNTR_ID)){
    dem$cont_exp[i]<-0
    next
  }
  else{
    x<-cont[cont$ENCNTR_ID == dem$ENCNTR_ID[i],]
    x<-x[dplyr::between(x = x$date, left = dem$tx_index[i]-
1, right = dem$tx_end[i]#
),]
    if(dim(x)[1]>0){
      dem$cont_exp[i]<-1
    }
    else{

```

```

    dem$cont_exp[i]<-0
  }
}

for(i in 1:nrow(dem)){
  if(!(dem$ENCNTR_ID [i] %in% nsaid$ENCNTR_ID)){
    dem$nsaid_exp[i]<-0
    next
  }
  else{
    x<-nsaid[nsaid$ENCNTR_ID == dem$ENCNTR_ID[i],]
    x<-x[dplyr::between(x = x$date, left = dem$tx_index[i]-
1, right = dem$tx_end[i]),]
    if(dim(x)[1]>0){
      dem$nsaid_exp[i]<-1
    }
    else{
      dem$nsaid_exp[i]<-0
    }
  }
}

for(i in 1:nrow(dem)){
  if(!(dem$ENCNTR_ID [i] %in% calc$ENCNTR_ID)){
    dem$calc_exp[i]<-0
    next
  }
  else{
    x<-calc[calc$ENCNTR_ID == dem$ENCNTR_ID[i],]
    x<-x[dplyr::between(x = x$date, left = dem$tx_index[i]-
1, right = dem$tx_end[i]#
),]
    if(dim(x)[1]>0){
      dem$calc_exp[i]<-1
    }
    else{
      dem$calc_exp[i]<-0
    }
  }
}

for(i in 1:nrow(dem)){
  if(!(dem$ENCNTR_ID [i] %in% loop$ENCNTR_ID)){
    dem$loop_exp[i]<-0
    next
  }
  else{
    x<-loop[loop$ENCNTR_ID == dem$ENCNTR_ID[i],]

```



```

    x<-x[dplyr::between(x = x$date, left = dem$tx_index[i]-
1, right = dem$tx_end[i]),]
    if(dim(x)[1]>0){
        dem$loop_exp[i]<-1
    }
    else{
        dem$loop_exp[i]<-0
    }
}
}

for(i in 1:nrow(dem)){
    if(!(dem$ENCNTR_ID [i] %in% vaso$ENCNTR_ID)){
        dem$vaso_exp[i]<-0
        next
    }
    else{
        x<-vaso[vaso$ENCNTR_ID == dem$ENCNTR_ID[i],]
        x<-x[dplyr::between(x = x$date, left = dem$tx_index[i]-
1, right = dem$tx_end[i]),]
        if(dim(x)[1]>0){
            dem$vaso_exp[i]<-1
        }
        else{
            dem$vaso_exp[i]<-0
        }
    }
}

for(i in 1:nrow(dem)){
    if(!(dem$ENCNTR_ID [i] %in% iono$ENCNTR_ID)){
        dem$iono_exp[i]<-0
        next
    }
    else{
        x<-iono[iono$ENCNTR_ID == dem$ENCNTR_ID[i],]
        x<-x[dplyr::between(x = x$date, left = dem$tx_index[i]-
1, right = dem$tx_end[i]),]
        if(dim(x)[1]>0){
            dem$iono_exp[i]<-1
        }
        else{
            dem$iono_exp[i]<-0
        }
    }
}

for(i in 1:nrow(dem)){
    if(!(dem$ENCNTR_ID [i] %in% acei$ENCNTR_ID)){

```

```

    dem$acei_exp[i]<-0
  next
}
else{
  x<-acei[acei$ENCNTR_ID == dem$ENCNTR_ID[i],]
  x<-x[dplyr::between(x = x$date, left = dem$tx_index[i]-
1, right = dem$tx_end[i]),]
  if(dim(x)[1]>0){
    dem$acei_exp[i]<-1
  }
  else{
    dem$acei_exp[i]<-0
  }
}
}
}

for(i in 1:nrow(dem)){
  if(!(dem$ENCNTR_ID [i] %in% arb$ENCNTR_ID)){
    dem$arb_exp[i]<-0
    next
  }
  else{
    x<-arb[arb$ENCNTR_ID == dem$ENCNTR_ID[i],]
    x<-x[dplyr::between(x = x$date, left = dem$tx_index[i]-
1, right = dem$tx_end[i]#
),]
    if(dim(x)[1]>0){
      dem$arb_exp[i]<-1
    }
    else{
      dem$arb_exp[i]<-0
    }
  }
}
}

#####
#####
##                               Vital signs clean up
##                               ##
#####
#####
vit<-
fread('///file2/crutter/UKHC - Cotner, Sarah - 2016/Cotner/cotner_vit
als.csv', sep=',', colClasses='character')
vit<-vit[vit$ENCNTR_ID %in% dem$ENCNTR_ID,]
bp<-
vit[grepl('Systolic', vit$LEFT_LABEL, ignore.case = T)| grepl('diast
olic', vit$LEFT_LABEL, ignore.case = T),]
bp$VAL_TXT<-as.numeric(bp$VAL_TXT)

```

```

bpcast<-
dcast.data.table(ENCNTR_ID+RECRD_DT_TM~LEFT_LABEL, value.var = 'VAL_
TXT', data=bp, fun.aggregate = min)
bpcast$dbp[is.infinite(bpcast$'Direct Arterial Blood Pressure (Diast
olic)')]<-bpcast$Diastolic
bpcast$sbp[is.infinite(bpcast$'Direct Arterial Blood Pressure (Systo
lic)')]<-bpcast$Systolic
bpcast$dbp[is.infinite(bpcast$Diastolic)]<-
bpcast$'Direct Arterial Blood Pressure (Diastolic)'
bpcast$sbp[is.infinite(bpcast$Systolic)]<-
bpcast$'Direct Arterial Blood Pressure (Systolic)'
bpcast$dbp[is.infinite(bpcast$'Direct Arterial Blood Pressure (Diast
olic)')& is.infinite(bpcast$Diastolic)]<-NA
bpcast$sbp[is.infinite(bpcast$'Direct Arterial Blood Pressure (Systo
lic)')& is.infinite(bpcast$Systolic)]<-NA
bpcast$dbp[is.infinite(bpcast$dbp)]<-NA
bpcast$sbp[is.infinite(bpcast$sbp)]<-NA
bp<-dplyr::select(bpcast, ENCNTR_ID, RECRD_DT_TM, dbp, sbp)

bp<-bp[complete.cases(bp),]
bp$date<-sapply(strsplit(bp$RECRD_DT_TM, ' '), '[',1)
bp$date<-as.Date(bp$date, format = '%d-%b-%y')
bp$RECRD_DT_TM<-as.POSIXct(bp$RECRD_DT_TM, format='%d-%b-
%y %H:%M:%S')

bp$map<-round((2*bp$dbp +bp$sbp)/3,2)
sbpcut<-mean(bp$sbp)+4*sd(bp$sbp)
dbpcut<-mean(bp$dbp)+4*sd(bp$dbp)
mapcut<-mean(bp$map)+4*sd(bp$map)
bp<-bp[bp$sbp<=sbpcut & bp$dbp <= dbpcut & bp$map<=mapcut,]

dem$hypotension<-0

for(i in 1:nrow(dem)){
  if(min(bp$map[bp$ENCNTR_ID == dem$ENCNTR_ID[i] & dplyr::between(bp
$date,
le
ft = dem$tx_index[i]-1,
ri
ght = dem$tx_end[i]))<65){
  dem$hypotension[i]<-1
  next
}
  if(min(sbp<-
bp$sbp[bp$ENCNTR_ID == dem$ENCNTR_ID[i] & dplyr::between(bp$date,
left = dem$tx_index[i]-1,
right = dem$tx_end[i]))<90){

```

```

    dem$hypotension[i]<-1
  next
}
if(dem$vaso_exp[i]==1){
  dem$hypotension[i]<-1
}
}
}

```

Inverse probability of treatment weights, model, and plots

```

dat<-dem[dem$vanc_exp==1,]
rm(list=setdiff(ls(), c('dat','dem','akitab','restab')))

dem_back<-dem
dem<-dat
#run restab results and AKI tab

library(ipw)
dat$pv[dat$drug=='PTZ']<-1
dat$pv[is.na(dat$pv)]<-0
temp<-ipwpoint(exposure = pv, family = 'binomial', link='logit',
               numerator = ~1,
               denominator = ~GENDR_CD_DES+dm +COMORBIDITY_SCORE+
                 as.factor(baseline_crcl_cat) + amphb_exp + cont_exp
               +
                 calc_exp + vaso_exp + hypotension,
               data= dat)

summary(temp$ipw.weights)

ipwplot(weights = temp$ipw.weights, logscale = F)
summary(temp$den.mod)

dat$sw<-temp$ipw.weights

library(survey)
msm<-
(svyglm(aki~pv, family=quasibinomial(), design=svydesign(~1, weights
= ~sw, data=dat)))
msm2<-
(svyglm(aki~pv, family=binomial(), design=svydesign(~1, weights = ~s
w, data=dat)))

cbind(msm1=exp(coef(msm)), msm2=exp(coef(msm2)))
cbind(msm1=exp(confint(msm)),msm2=exp(confint(msm2)))
summary(msm)

```

```

msm_test<-
(svyglm(aki~male, family=quasibinomial(), design=svydesign(~1, weights = ~sw, data=dat)))
summary(msm_test)

#####

library(ggplot2)
table(dat$aki, dat$drug)
table(dat$RIFLE, dat$drug)

x<-data.frame(drug = c('pv', 'pv', 'pv', 'pv',
                      'cv', 'cv', 'cv', 'cv'),
              class = c('n', 'r', 'i', 'f',
                        'n', 'r', 'i', 'f'),
              n = c(7185, 1516, 777, 420,
                    286, 33, 12, 7))

pv<-sum(x$n[x$drug=='pv'])
x$perc[x$drug=='pv']<-(x$n[x$drug=='pv']/pv)*100

cv<-sum(x$n[x$drug=='cv'])
x$perc[x$drug=='cv']<-(x$n[x$drug=='cv']/cv)*100

xadd<-data.frame(drug = c('pv',
                          'cv'),
                 class = c('aki',
                            'aki'),
                 n = c(pv-x$n[x$class=='n' & x$drug=='pv'],
                       cv-x$n[x$class=='n' & x$drug=='cv']),
                 perc = c(100-x$perc[x$class=='n' & x$drug=='pv'],
                          100-x$perc[x$class=='n' & x$drug=='cv'])
)

x<-rbind(x,xadd)
x<-x[x$class!='n',]
#####
library(ggplot2)

x$drug<-as.factor(x$drug)
x$drug<-relevel(x$drug, ref='pv')

p<-ggplot(x, aes(x=class, y=perc, fill=drug))

p + geom_bar(stat='identity', position= position_dodge(), color='black') +

```

```

xlab('AKI classification') +
ylab('Incidence (%)')+
scale_x_discrete(limits = c('aki', 'r', 'i', 'f'),
                 labels = c('Any AKI', 'Risk', 'Injury', 'Failure'))
+
scale_fill_grey(labels = c('TZP+VAN', 'MEM+VAN')) +
scale_y_continuous(expand = c(0,0),
                  limits = c(0,30),
                  breaks = seq(0,30, by = 5))+
theme_bw() +
annotate('text', x=0.8, y = 28.4, label = '27.4%', color = 'black',
size = 3) +
annotate('text', x=1.25, y = 16.4, label = '15.4%', color = 'black',
size = 3) +
annotate('text', x=1.8, y = 16.3, label = '15.3%', color = 'black',
size = 3) +
annotate('text', x=2.25, y = 10.8, label = '9.8%', color = 'black',
size = 3) +
annotate('text', x=2.8, y = 8.8, label = '7.8%', color = 'black', s
ize = 3) +
annotate('text', x=3.25, y = 4.5, label = '3.5%', color = 'black',
size = 3) +
annotate('text', x=3.8, y = 5.2, label = '4.2%', color = 'black', s
ize = 3) +
annotate('text', x=4.25, y = 3.1, label = '2.1%', color = 'black',
size = 3) +
theme(legend.position = 'bottom',
      legend.title = element_blank(),
      legend.text = element_text(color = 'black'),
      axis.text = element_text(color = 'black'),
      axis.title = element_text(color = 'black'),
      axis.ticks = element_blank())
ggsave('AKI plot.png', width = 4, height = 3, units = 'in', dpi = 120
0)
#####
#####

dat$dc_date<-sapply(strsplit(dat$DISCHRG_DT, ' '), '[' ,1)
dat$dc_date<-as.Date(dat$dc_date, format= '%d-%b-%y')
dat$LENGTH_OF_STAY_NUM[is.na(dat$LENGTH_OF_STAY_NUM)]<- as.numeric(d
at$dc_date[is.na(dat$LENGTH_OF_STAY_NUM)] -

dat$ad_date[is.na(dat$LENGTH_OF_STAY_NUM)])

quantiles_95 <- function(x) {
  r <- quantile(x, probs=c(0.05, 0.25, 0.5, 0.75, 0.95))
  names(r) <- c("ymin", "lower", "middle", "upper", "ymax")
  r
}

```

```

q<-ggplot(data=dat, aes(x = LENGTH_OF_STAY_NUM, fill=drug))

los_summary<-data.frame(drug = c('MEM', 'PTZ'),
                        mean = c(15.8, 14.5),
                        sd = c(27.6, 15.5),
                        median = c(9, 10),
                        l25 = c(6, 5),
                        u25 = c(15, 18),
                        l5 = c(3,3),
                        u95 = c(48.15, 41)
)

q+geom_boxplot(aes(middle = median, lower = l25, upper =u25, ymin =
15, ymax = u95), stat='identity') +
  scale_y_continuous(limits=c(0,50), breaks = seq(0,50, by=10), expan
nd = c(0,0)) +
  scale_x_discrete( labels = c('MEM+VAN', 'TZP+VAN'))+
  guides(fill=F) +
  stat_summary(fun.y = mean, geom='point', shape=18, size =4, na.rm=
T)+
  scale_fill_manual(values='light gray') +
  ylab('Length of stay (days)') +
  xlab('Drug therapy') +
  theme_bw()+
  theme(axis.ticks = element_blank(),
        axis.text = element_text(color = 'black'),
        axis.title = element_text(color='black', face='bold'))
q<-ggplot(los_summary, aes(x = drug, y=mean, fill='gray'))

q+geom_boxplot(aes(middle = median, lower = l25, upper =u25, ymin =
15, ymax = u95), stat='identity') +
  scale_y_continuous(limits=c(0,50), breaks = seq(0,50, by=10), expan
nd = c(0,0)) +
  scale_x_discrete( labels = c('MEM+VAN', 'TZP+VAN'))+
  guides(fill=F) +
  stat_summary(fun.y = mean, geom='point', shape=18, size =4, na.rm=
T)+
  scale_fill_manual(values='light gray') +
  ylab('Length of stay (days)') +
  xlab('Drug therapy') +
  theme_bw()+
  theme(axis.ticks = element_blank(),
        axis.text = element_text(color = 'black'),
        axis.title = element_text(color='black', face='bold'))

```

Data table generation

```
restab<-
data.frame(variable = rep(NA,100), MEM= NA, PTZ = NA, p=NA)
restab$variable[1] = 'N'
restab$MEM[1] = paste(nrow(dem[dem$drug=='MEM',]), " (", (round(nrow
(dem[dem$drug=='MEM',])/nrow(dem),3)*100), '%)', sep='')
restab$PTZ[1] = paste(nrow(dem[dem$drug=='PTZ',]), " (", (round(nrow
(dem[dem$drug=='PTZ',])/nrow(dem),3)*100), '%)', sep='')

attach(dem)

restab$variable[2]<-'Age (mean[SD])'
restab$MEM[2]<-
paste(round(mean(AGE[drug=='MEM'], na.rm = T),2), ' (', round(sd(AGE
[drug=='MEM'], na.rm = T),2), ')', sep='')
restab$PTZ[2]<-
paste(round(mean(AGE[drug=='PTZ'], na.rm = T),2), ' (', round(sd(AGE
[drug=='PTZ'], na.rm = T),2), ')', sep='')
restab$p[2]<-t.test(AGE~drug)$p.value

restab$variable[3]<-'Age (median [IQR])'
restab$MEM[3]<-
paste(median(AGE[drug=='MEM'], na.rm=T), " (", quantile(AGE[drug=='M
EM'], probs=0.25, na.rm = T), '- ',
      quantile(AGE[drug=='MEM'], probs=0.75, na.rm = T
), ')', sep='')
restab$PTZ[3]<-
paste(median(AGE[drug=='PTZ'], na.rm=T), " (", quantile(AGE[drug=='P
TZ'], probs=0.25, na.rm = T), '- ',
      quantile(AGE[drug=='PTZ'], probs=0.75, na.rm =
T), ')', sep='')
restab$p[3]<-wilcox.test(AGE~drug)$p.value

restab$variable[4]<-'Gender'
restab$variable[5]<-'Male'
restab$MEM[5]<-
paste(nrow(dem[dem$GENDR_CD_DES=='MALE' & dem$drug=='MEM',]), ' (',
      round((nrow(dem[dem$GENDR_CD_DES=='MALE' & dem$d
rug=='MEM',])/nrow(dem[dem$drug=='MEM',])*100),2), '%)', sep='')
restab$PTZ[5]<-
paste(nrow(dem[dem$GENDR_CD_DES=='MALE' & dem$drug=='PTZ',]), ' (',
      round((nrow(dem[dem$GENDR_CD_DES=='MALE' & dem$
drug=='PTZ',])/nrow(dem[dem$drug=='PTZ',])*100),2), '%)', sep='')
restab$variable[6]<-'Female'
```



```

restab$MEM[6]<-
paste(nrow(dem[dem$GENDR_CD_DES=='FEMALE' & dem$drug=='MEM',]), ' ('
,
      round((nrow(dem[dem$GENDR_CD_DES=='FEMALE' & dem
$drug=='MEM',])/nrow(dem[dem$drug=='MEM',])*100),2), '%)', sep='')
restab$PTZ[6]<-
paste(nrow(dem[dem$GENDR_CD_DES=='FEMALE' & dem$drug=='PTZ',]), ' ('
,
      round((nrow(dem[dem$GENDR_CD_DES=='FEMALE' & de
m$drug=='PTZ',])/nrow(dem[dem$drug=='PTZ',])*100),2), '%)', sep='')
restab$p[4]<-chisq.test(table(GENDR_CD_DES, drug))$p.value

restab$variable[7]<-'caucasian'
restab$MEM[7]<-
paste(nrow(dem[dem$caucasian==1 & dem$drug=='MEM',]), ' ('
      round((nrow(dem[dem$caucasian==1 & dem$drug=='ME
M',])/nrow(dem[dem$drug=='MEM',])*100),2), '%)', sep='')
restab$PTZ[7]<-
paste(nrow(dem[dem$caucasian==1 & dem$drug=='PTZ',]), ' ('
      round((nrow(dem[dem$caucasian==1 & dem$drug=='P
TZ',])/nrow(dem[dem$drug=='PTZ',])*100),2), '%)', sep='')
restab$p[7]<-chisq.test(table(caucasian, drug))$p.value

restab$variable[8]<-'WT (mean[SD])'
restab$MEM[8]<-
paste(round(mean(INIT_WT[drug=='MEM'], na.rm = T),2), ' ('
round(sd
(INIT_WT[drug=='MEM'], na.rm = T),2), ')', sep='')
restab$PTZ[8]<-
paste(round(mean(INIT_WT[drug=='PTZ'], na.rm = T),2), ' ('
round(sd
(INIT_WT[drug=='PTZ'], na.rm = T),2), ')', sep='')
restab$p[8]<-t.test(INIT_WT~drug)$p.value

restab$variable[9]<-'WT (median [IQR])'
restab$MEM[9]<-
paste(median(INIT_WT[drug=='MEM'], na.rm=T), " ("
, quantile(INIT_WT[
drug=='MEM'], probs=0.25, na.rm = T), '- '
      , quantile(INIT_WT[drug=='MEM'], probs=0.75, na.rm
= T), ')', sep='')
restab$PTZ[9]<-
paste(median(INIT_WT[drug=='PTZ'], na.rm=T), " ("
, quantile(INIT_WT[
drug=='PTZ'], probs=0.25, na.rm = T), '- '
      , quantile(INIT_WT[drug=='PTZ'], probs=0.75, na.r
m = T), ')', sep='')
restab$p[9]<-wilcox.test(INIT_WT~drug)$p.value

restab$variable[10]<-'BMI (mean[SD])'

```

```

restab$MEM[10]<-
paste(round(mean(BMI[drug=='MEM'], na.rm = T),2), ' (', round(sd(BMI
[drug=='MEM'], na.rm = T),2), ')', sep='')
restab$PTZ[10]<-
paste(round(mean(BMI[drug=='PTZ'], na.rm = T),2), ' (', round(sd(BMI
[drug=='PTZ'], na.rm = T),2), ')', sep='')
restab$p[10]<-t.test(BMI~drug)$p.value

restab$variable[11]<- 'BMI (median [IQR])'
restab$MEM[11]<-
paste(round(median(BMI[drug=='MEM'], na.rm=T),2), " (", round(quantile
(BMI[drug=='MEM'], probs=0.25, na.rm = T),2), '- ',
round(quantile(BMI[drug=='MEM'], probs=0.75, na
.rm = T),2), ')', sep='')
restab$PTZ[11]<-
paste(round(median(BMI[drug=='PTZ'], na.rm=T),2), " (", round(quantile
(BMI[drug=='PTZ'], probs=0.25, na.rm = T),2), '- ',
round(quantile(BMI[drug=='PTZ'], probs=0.75, n
a.rm = T),2), ')', sep='')
restab$p[11]<-wilcox.test(BMI~drug)$p.value

restab$variable[12]<- 'COMORBIDITY_SCORE (mean[SD])'
restab$MEM[12]<-
paste(round(mean(dem$COMORBIDITY_SCORE[drug=='MEM'], na.rm = T),2),
' (', round(sd(dem$COMORBIDITY_SCORE[drug=='MEM'], na.rm = T),2), ')',
, sep='')
restab$PTZ[12]<-
paste(round(mean(dem$COMORBIDITY_SCORE[drug=='PTZ'], na.rm = T),2),
' (', round(sd(dem$COMORBIDITY_SCORE[drug=='PTZ'], na.rm = T),2), ')',
, sep='')
restab$p[12]<-t.test(dem$COMORBIDITY_SCORE~drug)$p.value

restab$variable[13]<- 'COMORBIDITY_SCORE (median [IQR])'
restab$MEM[13]<-
paste(median(dem$COMORBIDITY_SCORE[drug=='MEM'], na.rm=T), " (", qua
ntile(dem$COMORBIDITY_SCORE[drug=='MEM'], probs=0.25, na.rm = T), '-
',
quantile(dem$COMORBIDITY_SCORE[drug=='MEM'], pr
obs=0.75, na.rm = T), ')', sep='')
restab$PTZ[13]<-
paste(median(dem$COMORBIDITY_SCORE[drug=='PTZ'], na.rm=T), " (", qua
ntile(dem$COMORBIDITY_SCORE[drug=='PTZ'], probs=0.25, na.rm = T), '-
',
quantile(dem$COMORBIDITY_SCORE[drug=='PTZ'], p
robs=0.75, na.rm = T), ')', sep='')
restab$p[13]<-wilcox.test(dem$COMORBIDITY_SCORE~drug)$p.value

restab$variable[14]<- 'baseline crcl (mean[SD])'

```

```

restab$MEM[14]<-
paste(round(mean(dem$baseline_crcl[drug=='MEM'], na.rm = T),2), ' ('
, round(sd(dem$baseline_crcl[drug=='MEM'], na.rm = T),2), ')', sep='''
)
restab$PTZ[14]<-
paste(round(mean(dem$baseline_crcl[drug=='PTZ'], na.rm = T),2), ' ('
, round(sd(dem$baseline_crcl[drug=='PTZ'], na.rm = T),2), ')', sep='''
)
restab$p[14]<-t.test(dem$baseline_crcl~drug)$p.value

restab$variable[15]<- 'baseline crcl (median [IQR])'
restab$MEM[15]<-
paste(round(median(dem$baseline_crcl[drug=='MEM'], na.rm=T),2), " ("
,
          round(quantile(dem$baseline_crcl[drug=='MEM'],
probs=0.25, na.rm = T),2), '- ',
          round(quantile(dem$baseline_crcl[drug=='MEM'],
probs=0.75, na.rm = T),2), ')', sep='')
restab$PTZ[15]<-
paste(round(median(dem$baseline_crcl[drug=='PTZ'], na.rm=T),2), " ("
,
          round(quantile(dem$baseline_crcl[drug=='PTZ'],
probs=0.25, na.rm = T),2), '- ',
          round(quantile(dem$baseline_crcl[drug=='PTZ'],
probs=0.75, na.rm = T),2), ')', sep='')
restab$p[15]<-wilcox.test(dem$baseline_crcl~drug)$p.value

restab$variable[16]<- 'baseline crcl drug'
restab$variable[17]<- '30-59 mL/min'
restab$MEM[17]<-
paste(nrow(dem[dem$baseline_crcl_cat == 1 & dem$drug=='MEM',]), ' ('
,
          round((nrow(dem[dem$baseline_crcl_cat == 1 & de
m$drug=='MEM',])/nrow(dem[dem$drug=='MEM',])*100),2), '%)', sep='')

restab$PTZ[17]<-
paste(nrow(dem[dem$baseline_crcl_cat == 1 & dem$drug=='PTZ',]), ' ('
,
          round((nrow(dem[dem$baseline_crcl_cat == 1 & d
em$drug=='PTZ',])/nrow(dem[dem$drug=='PTZ',])*100),2), '%)', sep='')

restab$variable[18]<- '60-89 mL/min'
restab$MEM[18]<-
paste(nrow(dem[dem$baseline_crcl_cat == 2 & dem$drug=='MEM',]), ' ('
,
          round((nrow(dem[dem$baseline_crcl_cat == 2 & de
m$drug=='MEM',])/nrow(dem[dem$drug=='MEM',])*100),2), '%)', sep='')

```

```

restab$PTZ[18]<-
paste(nrow(dem[dem$baseline_crcl_cat == 2 & dem$drug=='PTZ',]), ' ( '
,
      round((nrow(dem[dem$baseline_crcl_cat == 2 & d
dem$drug=='PTZ',])/nrow(dem[dem$drug=='PTZ',])*100),2), '%)', sep='')

restab$variable[19]<- '>=90 mL/min'
restab$MEM[19]<-
paste(nrow(dem[dem$baseline_crcl_cat == 3 & dem$drug=='MEM',]), ' ( '
,
      round((nrow(dem[dem$baseline_crcl_cat == 3 & de
m$drug=='MEM',])/nrow(dem[dem$drug=='MEM',])*100),2), '%)', sep='')

restab$PTZ[19]<-
paste(nrow(dem[dem$baseline_crcl_cat == 3 & dem$drug=='PTZ',]), ' ( '
,
      round((nrow(dem[dem$baseline_crcl_cat == 3 & d
dem$drug=='PTZ',])/nrow(dem[dem$drug=='PTZ',])*100),2), '%)', sep='')

restab$p[16]<-chisq.test(table(baseline_crcl_cat, drug))$p.value

restab$variable[20]<- 'Concomitant nephrotoxins'
restab$variable[21]<- 'Aminoglycosides'
restab$MEM[21]<-
paste(nrow(dem[dem$aminoglycoside_exp == 1 & dem$drug=='MEM',]), ' ( '
,
      round((nrow(dem[dem$aminoglycoside_exp == 1 & d
dem$drug=='MEM',])/nrow(dem[dem$drug=='MEM',])*100),2),
      '%)', sep='')

restab$PTZ[21]<-
paste(nrow(dem[dem$aminoglycoside_exp == 1 & dem$drug=='PTZ',]), ' ( '
,
      round((nrow(dem[dem$aminoglycoside_exp == 1 &
dem$drug=='PTZ',])/nrow(dem[dem$drug=='PTZ',])*100),2),
      '%)', sep='')
restab$p[21]<-chisq.test(table(aminoglycoside_exp, drug))$p.value

restab$variable[22]<- 'amphb'
restab$MEM[22]<-
paste(nrow(dem[dem$amphb_exp == 1 & dem$drug=='MEM',]), ' ( '
,
      round((nrow(dem[dem$amphb_exp == 1 & dem$drug==
'MEM',])/nrow(dem[dem$drug=='MEM',])*100),2),
      '%)', sep='')

restab$PTZ[22]<-
paste(nrow(dem[dem$amphb_exp == 1 & dem$drug=='PTZ',]), ' ( '
,
      round((nrow(dem[dem$amphb_exp == 1 & dem$drug=
'PTZ',])/nrow(dem[dem$drug=='PTZ',])*100),2),
      '%)', sep='')
restab$p[22]<-chisq.test(table(amphb_exp, drug))$p.value

```

```

restab$variable[23]<- 'acei'
restab$MEM[23]<-
paste(nrow(dem[dem$acei_exp == 1 & dem$drug=='MEM',]), ' (',
      round((nrow(dem[dem$acei_exp == 1 & dem$drug=='
MEM', ])/nrow(dem[dem$drug=='MEM', ])*100),2),
      '%)', sep='')
restab$PTZ[23]<-
paste(nrow(dem[dem$acei_exp == 1 & dem$drug=='PTZ',]), ' (',
      round((nrow(dem[dem$acei_exp == 1 & dem$drug=='
'PTZ', ])/nrow(dem[dem$drug=='PTZ', ])*100),2),
      '%)', sep='')
restab$p[23]<-chisq.test(table(acei_exp, drug))$p.value

restab$variable[24]<- 'arb'
restab$MEM[24]<-
paste(nrow(dem[dem$arb_exp == 1 & dem$drug=='MEM',]), ' (',
      round((nrow(dem[dem$arb_exp == 1 & dem$drug=='M
EM', ])/nrow(dem[dem$drug=='MEM', ])*100),2),
      '%)', sep='')
restab$PTZ[24]<-
paste(nrow(dem[dem$arb_exp == 1 & dem$drug=='PTZ',]), ' (',
      round((nrow(dem[dem$arb_exp == 1 & dem$drug=='
PTZ', ])/nrow(dem[dem$drug=='PTZ', ])*100),2),
      '%)', sep='')
restab$p[24]<-chisq.test(table(arb_exp, drug))$p.value

restab$variable[25]<- 'cont'
restab$MEM[25]<-
paste(nrow(dem[dem$cont_exp == 1 & dem$drug=='MEM',]), ' (',
      round((nrow(dem[dem$cont_exp == 1 & dem$drug=='
MEM', ])/nrow(dem[dem$drug=='MEM', ])*100),2),
      '%)', sep='')
restab$PTZ[25]<-
paste(nrow(dem[dem$cont_exp == 1 & dem$drug=='PTZ',]), ' (',
      round((nrow(dem[dem$cont_exp == 1 & dem$drug=='
'PTZ', ])/nrow(dem[dem$drug=='PTZ', ])*100),2),
      '%)', sep='')
restab$p[25]<-chisq.test(table(cont_exp, drug))$p.value

restab$variable[26]<- 'loop'
restab$MEM[26]<-
paste(nrow(dem[dem$loop_exp == 1 & dem$drug=='MEM',]), ' (',
      round((nrow(dem[dem$loop_exp == 1 & dem$drug=='
MEM', ])/nrow(dem[dem$drug=='MEM', ])*100),2),
      '%)', sep='')
restab$PTZ[26]<-
paste(nrow(dem[dem$loop_exp == 1 & dem$drug=='PTZ',]), ' (',

```

```

round((nrow(dem[dem$loop_exp == 1 & dem$drug==
'PTZ', ])/nrow(dem[dem$drug=='PTZ', ])*100),2),
      '%)', sep='')
restab$p[26]<-chisq.test(table(loop_exp, drug))$p.value

restab$variable[27]<-'nsaids'
restab$MEM[27]<-
paste(nrow(dem[dem$nsaids_exp == 1 & dem$drug=='MEM', ]), ' (',
      round((nrow(dem[dem$nsaids_exp == 1 & dem$drug=
='MEM', ])/nrow(dem[dem$drug=='MEM', ])*100),2),
      '%)', sep='')
restab$PTZ[27]<-
paste(nrow(dem[dem$nsaids_exp == 1 & dem$drug=='PTZ', ]), ' (',
      round((nrow(dem[dem$nsaids_exp == 1 & dem$drug
=='PTZ', ])/nrow(dem[dem$drug=='PTZ', ])*100),2),
      '%)', sep='')
restab$p[27]<-chisq.test(table(nsaids_exp, drug))$p.value

restab$variable[28]<-'calc'
restab$MEM[28]<-
paste(nrow(dem[dem$calc_exp == 1 & dem$drug=='MEM', ]), ' (',
      round((nrow(dem[dem$calc_exp == 1 & dem$drug=='
MEM', ])/nrow(dem[dem$drug=='MEM', ])*100),2),
      '%)', sep='')
restab$PTZ[28]<-
paste(nrow(dem[dem$calc_exp == 1 & dem$drug=='PTZ', ]), ' (',
      round((nrow(dem[dem$calc_exp == 1 & dem$drug==
'PTZ', ])/nrow(dem[dem$drug=='PTZ', ])*100),2),
      '%)', sep='')
restab$p[28]<-chisq.test(table(calc_exp, drug))$p.value

restab$variable[29]<-'vanc'
restab$MEM[29]<-
paste(nrow(dem[dem$vanc_exp == 1 & dem$drug=='MEM', ]), ' (',
      round((nrow(dem[dem$vanc_exp == 1 & dem$drug=='
MEM', ])/nrow(dem[dem$drug=='MEM', ])*100),2),
      '%)', sep='')
restab$PTZ[29]<-
paste(nrow(dem[dem$vanc_exp == 1 & dem$drug=='PTZ', ]), ' (',
      round((nrow(dem[dem$vanc_exp == 1 & dem$drug
=='PTZ', ])/nrow(dem[dem$drug=='PTZ', ])*100),2),
      '%)', sep='')
restab$p[29]<-chisq.test(table(vanc_exp, drug))$p.value

restab$variable[30]<-'vaso'
restab$MEM[30]<-
paste(nrow(dem[dem$vaso_exp == 1 & dem$drug=='MEM', ]), ' (',
      round((nrow(dem[dem$vaso_exp == 1 & dem$drug=='
MEM', ])/nrow(dem[dem$drug=='MEM', ])*100),2),

```

```

                                '%)', sep='')
restab$PTZ[30]<-
paste(nrow(dem[dem$vaso_exp == 1 & dem$drug=='PTZ',]), ' (',
      round((nrow(dem[dem$vaso_exp == 1 & dem$drug=='
'PTZ', ])/nrow(dem[dem$drug=='PTZ', ])*100),2),
      '%)', sep='')
restab$p[30]<-chisq.test(table(vaso_exp, drug))$p.value

restab$variable[31]<- 'Comorbidities'
restab$variable[32]<- 'DM'
restab$MEM[32]<-
paste(nrow(dem[dem$dm==1 & dem$drug=='MEM',]), ' (',
      round((nrow(dem[dem$dm==1 & dem$drug=='MEM', ])/
nrow(dem[dem$drug=='MEM', ])*100),2), '%)', sep='')
restab$PTZ[32]<-
paste(nrow(dem[dem$dm==1 & dem$drug=='PTZ',]), ' (',
      round((nrow(dem[dem$dm==1 & dem$drug=='PTZ', ]
)/nrow(dem[dem$drug=='PTZ', ])*100),2), '%)', sep='')
restab$p[32]<-chisq.test(table(dem$dm, drug))$p.value

restab$variable[33]<- 'HF'
restab$MEM[33]<-
paste(nrow(dem[dem$hf==1 & dem$drug=='MEM',]), ' (',
      round((nrow(dem[dem$hf==1 & dem$drug=='MEM', ])/
nrow(dem[dem$drug=='MEM', ])*100),2), '%)', sep='')
restab$PTZ[33]<-
paste(nrow(dem[dem$hf==1 & dem$drug=='PTZ',]), ' (',
      round((nrow(dem[dem$hf==1 & dem$drug=='PTZ', ]
)/nrow(dem[dem$drug=='PTZ', ])*100),2), '%)', sep='')
restab$p[33]<-chisq.test(table(dem$hf, drug))$p.value

restab$variable[34]<- 'HTN'
restab$MEM[34]<-
paste(nrow(dem[dem$HTN==1 & dem$drug=='MEM',]), ' (',
      round((nrow(dem[dem$HTN==1 & dem$drug=='MEM', ]
)/nrow(dem[dem$drug=='MEM', ])*100),2), '%)', sep='')
restab$PTZ[34]<-
paste(nrow(dem[dem$HTN==1 & dem$drug=='PTZ',]), ' (',
      round((nrow(dem[dem$HTN==1 & dem$drug=='PTZ', ]
)/nrow(dem[dem$drug=='PTZ', ])*100),2), '%)', sep='')
restab$p[34]<-chisq.test(table(HTN, drug))$p.value

restab$variable[35]<- 'CF'
restab$MEM[35]<-
paste(nrow(dem[dem$CF==1 & dem$drug=='MEM',]), ' (',
      round((nrow(dem[dem$CF==1 & dem$drug=='MEM', ])/
nrow(dem[dem$drug=='MEM', ])*100),2), '%)', sep='')
restab$PTZ[35]<-
paste(nrow(dem[dem$CF==1 & dem$drug=='PTZ',]), ' (',

```

```

        round((nrow(dem[dem$CF==1 & dem$drug=='PTZ',])
/nrow(dem[dem$drug=='PTZ',])*100),2), '%', sep='')
restab$p[35]<-chisq.test(table(CF, drug))$p.value

restab$variable[36]<- 'LOS (mean[SD])'
restab$MEM[36]<-
paste(round(mean(dem$LENGTH_OF_STAY_NUM[drug=='MEM'], na.rm = T),2),
'(', round(sd(dem$LENGTH_OF_STAY_NUM[drug=='MEM'], na.rm = T),2),
')', sep='')
restab$PTZ[36]<-
paste(round(mean(dem$LENGTH_OF_STAY_NUM[drug=='PTZ'], na.rm = T),2),
'(', round(sd(dem$LENGTH_OF_STAY_NUM[drug=='PTZ'], na.rm = T),2),
')', sep='')
restab$p[36]<-t.test(dem$LENGTH_OF_STAY_NUM~drug)$p.value

restab$variable[37]<- 'LOS (median [IQR])'
restab$MEM[37]<-
paste(median(dem$LENGTH_OF_STAY_NUM[drug=='MEM'], na.rm=T), "(", qu
antile(dem$LENGTH_OF_STAY_NUM[drug=='MEM'], probs=0.25, na.rm = T), '
-',
        quantile(dem$LENGTH_OF_STAY_NUM[drug=='MEM'], p
robs=0.75, na.rm = T), ')', sep='')
restab$PTZ[37]<-
paste(median(dem$LENGTH_OF_STAY_NUM[drug=='PTZ'], na.rm=T), "(", qu
antile(dem$LENGTH_OF_STAY_NUM[drug=='PTZ'], probs=0.25, na.rm = T), '
-',
        quantile(dem$LENGTH_OF_STAY_NUM[drug=='PTZ'],
probs=0.75, na.rm = T), ')', sep='')
restab$p[37]<-wilcox.test(dem$LENGTH_OF_STAY_NUM~drug)$p.value

# restab$variable[38]<- 'icu_admit'
# restab$MEM[38]<-
paste(nrow(dem[dem$icu_admit==1 & dem$drug=='MEM',]), '(',
#
        round((nrow(dem[dem$icu_admit==1 & dem$drug==
'MEM',])/nrow(dem[dem$drug=='MEM',])*100),2), '%', sep='')
# restab$PTZ[38]<-
paste(nrow(dem[dem$icu_admit==1 & dem$drug=='PTZ',]), '(',
#
        round((nrow(dem[dem$icu_admit==1 & dem$dru
g=='PTZ',])/nrow(dem[dem$drug=='PTZ',])*100),2), '%', sep='')
# restab$p[38]<-chisq.test(table(icu_admit, drug))$p.value

# restab$variable[39]<- 'Drug'
# restab$variable[40]<- 'PTZ'
# restab$MEM[40]<-
paste(nrow(dem[dem$drug=='P' & dem$drug=='MEM',]), '(',
#
        round((nrow(dem[dem$drug=='P' & dem$drug=='ME
M',])/nrow(dem[dem$drug=='MEM',])*100),2), '%', sep='')
# restab$PTZ[40]<-
paste(nrow(dem[dem$drug=='P' & dem$drug=='PTZ',]), '(',

```



```

#           round((nrow(dem[dem$drug=='P' & dem$drug==
'PTZ',])/nrow(dem[dem$drug=='PTZ',])*100),2), '%', sep='')
# restab$variable[41]<- 'CFP'
# restab$MEM[41]<-
paste(nrow(dem[dem$drug=='C' & dem$drug=='MEM',]), ' (',
#           round((nrow(dem[dem$drug=='C' & dem$drug=='ME
M',])/nrow(dem[dem$drug=='MEM',])*100),2), '%', sep='')
# restab$PTZ[41]<-
paste(nrow(dem[dem$drug=='C' & dem$drug=='PTZ',]), ' (',
#           round((nrow(dem[dem$drug=='C' & dem$drug==
'PTZ',])/nrow(dem[dem$drug=='PTZ',])*100),2), '%', sep='')
# restab$variable[42]<- 'MEM'
# restab$MEM[42]<-
paste(nrow(dem[dem$drug=='M' & dem$drug=='MEM',]), ' (',
#           round((nrow(dem[dem$drug=='M' & dem$drug=='ME
M',])/nrow(dem[dem$drug=='MEM',])*100),2), '%', sep='')
# restab$PTZ[42]<-
paste(nrow(dem[dem$drug=='M' & dem$drug=='PTZ',]), ' (',
#           round((nrow(dem[dem$drug=='M' & dem$drug==
'PTZ',])/nrow(dem[dem$drug=='PTZ',])*100),2), '%', sep='')
#
# restab$p[39]<-chisq.test(table(drug, drug))$p.value

restab$variable[45]<- 'AKI'
restab$variable[46]<- 'Any'
restab$MEM[46]<-
paste(nrow(dem[dem$aki==1 & dem$drug=='MEM',]), ' (',
#           round((nrow(dem[dem$aki==1 & dem$drug=='MEM',])
/nrow(dem[dem$drug=='MEM',])*100),2), '%', sep='')
restab$PTZ[46]<-
paste(nrow(dem[dem$aki==1 & dem$drug=='PTZ',]), ' (',
#           round((nrow(dem[dem$aki==1 & dem$drug=='PTZ',]
)/nrow(dem[dem$drug=='PTZ',])*100),2), '%', sep='')
restab$p[46]<-chisq.test(table(aki, drug))$p.value

restab$variable[47]<- 'Risk'
restab$MEM[47]<-
paste(nrow(dem[dem$RIFLE=='risk' & dem$drug=='MEM',]), ' (',
#           round((nrow(dem[dem$RIFLE=='risk' & dem$drug==
MEM',])/nrow(dem[dem$drug=='MEM',])*100),2), '%', sep='')
restab$PTZ[47]<-
paste(nrow(dem[dem$RIFLE=='risk' & dem$drug=='PTZ',]), ' (',
#           round((nrow(dem[dem$RIFLE=='risk' & dem$drug==
'PTZ',])/nrow(dem[dem$drug=='PTZ',])*100),2), '%', sep='')
restab$variable[48]<- 'injury'
restab$MEM[48]<-
paste(nrow(dem[dem$RIFLE=='injury' & dem$drug=='MEM',]), ' (',
#           round((nrow(dem[dem$RIFLE=='injury' & dem$drug=
='MEM',])/nrow(dem[dem$drug=='MEM',])*100),2), '%', sep='')

```

```

restab$PTZ[48]<-
paste(nrow(dem[dem$RIFLE=='injury' & dem$drug=='PTZ',]), ' (',
      round((nrow(dem[dem$RIFLE=='injury' & dem$drug
=='PTZ',])/nrow(dem[dem$drug=='PTZ',])*100),2), '%)', sep='')

restab$variable[49]<-'failure'
restab$MEM[49]<-
paste(nrow(dem[dem$RIFLE=='failure' & dem$drug=='MEM',]), ' (',
      round((nrow(dem[dem$RIFLE=='failure' & dem$drug
=='MEM',])/nrow(dem[dem$drug=='MEM',])*100),2), '%)', sep='')
restab$PTZ[49]<-
paste(nrow(dem[dem$RIFLE=='failure' & dem$drug=='PTZ',]), ' (',
      round((nrow(dem[dem$RIFLE=='failure' & dem$dru
g=='PTZ',])/nrow(dem[dem$drug=='PTZ',])*100),2), '%)', sep='')

restab<-restab[!is.na(restab$variable),]
restab$p[restab$p <=0.00001]<-0.00001
restab$p<-round(restab$p, 5)
write.csv(restab,'unmatched_results_table.csv', row.names=F)
detach(dem)

```

Appendix C: Chapter 4 code

Data wrangling

```
library(plyr)
library(dplyr)
library(data.table)
dat<-
read.csv('//file2/crutter/UKHC - Cotner, Sarah - 2016/Cotner/cotner_
drugs.csv', sep=',', colClasses='character')
dem<-
fread('//file2/crutter/UKHC - Cotner, Sarah - 2016/Cotner/cotner_dem
o.csv',
      sep=',', colClasses='character')
dx<-
fread('//file2/crutter/UKHC - Cotner, Sarah - 2016/Cotner/COTNER_DX2
016-02-17 11-41-11.csv',
      sep=',', colClasses='character')
ht<-
fread('//file2/crutter/UKHC - Cotner, Sarah - 2016/Cotner/COTNER_HT_
WT2016-02-17 11-42-07.csv', sep=',',
      colClasses='character')
asid<-
unique(dat$ENCNTR_ID[grepl('sulbactam', dat$NAME, ignore.case = T)])
merid<-
unique(dat$ENCNTR_ID[grepl('meropenem', dat$NAME, ignore.case = T)])
pipid<-
unique(dat$ENCNTR_ID[grepl('piperacillin', dat$NAME, ignore.case = T
)])
cfpid<-
unique(dat$ENCNTR_ID[grepl('cefepime', dat$NAME, ignore.case = T)])
aspip<-intersect(asid, pipid)
ascfp<-intersect(asid, cfpid)
asmem<-intersect(asid, merid)
aspipcfp<-intersect(aspip, ascfp)
aspipmem<-intersect(aspip, asmem)
ascfpmem<-intersect(ascfp, asmem)
aspipcfpmem<-intersect(ascfpmem, aspipmem)
cfpmem<-intersect(cfpid, merid)
cfppip<-intersect(cfpid, pipid)
cfpmempip<-intersect(cfpmem, cfppip)
pipmem<-intersect(pipid, merid)
```

```

test<-
unique(dat$ENCNTR_ID[dat$ENCNTR_ID %in% asid | dat$ENCNTR_ID %in% me
rid | dat$ENCNTR_ID %in% pipid | dat$ENCNTR_ID %in% cfpid])
df<-data.frame(EID = test, group = NA)

df$group[df$EID %in% asid]<- 'A'
df$group[df$EID %in% cfpid]<- 'C'
df$group[df$EID %in% pipid]<- 'P'
df$group[df$EID %in% merid]<- 'M'
df$group[df$EID %in% aspip]<- 'AP'
df$group[df$EID %in% ascfp]<- 'AC'
df$group[df$EID %in% asmem]<- 'AM'
df$group[df$EID %in% cfpmem]<- 'CM'
df$group[df$EID %in% cfppip]<- 'CP'
df$group[df$EID %in% pipmem]<- 'MP'
df$group[df$EID %in% aspipmem]<- 'AMP'
df$group[df$EID %in% ascfpmem]<- 'ACM'
df$group[df$EID %in% aspipcfp]<- 'ACP'
df$group[df$EID %in% cfpmempip]<- 'CMP'
df$group[df$EID %in% aspipcfpmem]<- 'ACMP'

a_final=as.character(df$EID[df$group=='A'])
p_final=as.character(df$EID[df$group=='P'])
rm(asid, cfpid, pipid, merid, aspip, ascfp, asmem, cfpmem, cfppip, p
ipmem, aspipmem, ascfpmem, aspipcfp, aspipcfpmem, cfpmempip, test)
#####
#####
##                               Demographics clean up
##                               ##
#####
#####
dem<-dem[dem$ENCNTR_ID %in% a_final | dem$ENCNTR_ID %in% p_final,]
dem$drug[dem$ENCNTR_ID %in% a_final]<- 'AS'
dem$drug[dem$ENCNTR_ID %in% p_final]<- 'PTZ'
dem<-dem[!duplicated(dem$ENCNTR_ID),]

dem$ad_date<-sapply(strsplit(dem$ADMT_DT, ' '), '[' ,1)
dem$ad_date<-as.Date(dem$ad_date, format='%d-%b-%y')

dem<-dem[dplyr:::between(dem$ad_date,
                        left = as.Date('2006-07-01'),
                        right = as.Date('2015-09-30')
                        #incbounds = T
),]
dem$COMORBIDITY_SCORE<-as.numeric(dem$COMORBIDITY_SCORE)
dem$COMORBIDITY_SCORE[is.na(dem$COMORBIDITY_SCORE)]<-0
dem$AGE<-as.numeric(dem$AGE)
dem<-dem[dem$AGE >= 18,]
dem$age_group[dem$AGE<45]<- '18-44'

```

```

dem$age_group[dem$AGE>=45 & dem$AGE <65]<- '45-64'
dem$age_group[dem$AGE>=65 & dem$AGE <80]<- '65-79'
dem$age_group[dem$AGE>=80]<- '80+'

dem$LENGTH_OF_STAY_NUM<-as.numeric(dem$LENGTH_OF_STAY_NUM)

pregeid<-
unique(dx$FULL_ENCNR_ID[grepl('v22',dx$DX_CD, ignore.case = T)])
dem<-dem[!(dem$ENCNR_ID %in% pregeid),]

ckdeid<-
unique(dx$FULL_ENCNR_ID[grepl('585\\.[12349]', dx$DX_CD, ignore.case = T)])
dem<-dem[!(dem$ENCNR_ID %in% ckdeid),]

cf<-
unique(dx$FULL_ENCNR_ID[grepl('277\\. ', dx$DX_CD, ignore.case = T)])
)
dem$CF[dem$ENCNR_ID %in% cf]<-1
dem$CF[is.na(dem$CF)]<-0
dem<-dem[dem$CF==0,]

htn<-
unique(dx$FULL_ENCNR_ID[grepl('401\\. ', dx$DX_CD, ignore.case = T)])
)
dem$HTN[dem$ENCNR_ID %in% htn]<-1
dem$HTN[is.na(dem$HTN)]<-0

dm<-
unique(dx$FULL_ENCNR_ID[grepl('250\\. ', dx$DX_CD, ignore.case = T)])
)
dem$dm[dem$ENCNR_ID %in% dm]<-1
dem$dm[is.na(dem$dm)]<-0

hf<-
unique(dx$FULL_ENCNR_ID[grepl('428\\. ', dx$DX_CD, ignore.case = T)])
)
dem$hf[dem$ENCNR_ID %in% hf]<-1
dem$hf[is.na(dem$hf)]<-0

ht<-ht[ht$ENCNR_ID %in% dem$ENCNR_ID,]
ht$INIT_WT<-as.numeric(ht$INIT_WT)
ht$HT<-as.numeric(ht$HT)
ht$WT<-as.numeric(ht$WT)
ht$INIT_WT[is.na(ht$INIT_WT)]<-ht$WT[is.na(ht$INIT_WT)]
ht2<-select(ht, ENCNR_ID, INIT_WT, HT)

dem<-merge(dem, ht2, by='ENCNR_ID', all=T)
dem$INIT_WT[dem$INIT_WT==0]<-NA

```

```

dem$HT[dem$HT==0]<-NA

wtcut<-mean(dem$INIT_WT, na.rm=T)+4*sd(dem$INIT_WT, na.rm=T)
dem<-dem[dem$INIT_WT<=wtcut | is.na(dem$INIT_WT),]
htcut<-mean(dem$HT, na.rm=T)+4*sd(dem$HT, na.rm=T)
dem<-dem[dem$HT<=htcut | is.na(dem$HT),]
dem<-dem[dem$HT>27 | is.na(dem$HT),]

dem$BMI<-dem$INIT_WT/((dem$HT/100)**2)
rm(ckdeid, pregeid, ht, ht2, wtcut, htcut, dm, hf, htn,a_final, p_fi
nal, cf, df, crcl_cut)
#####
#####
##                               Medications clean up
##                               ##
#####
#####
meds<-dat
rm(dat)
meds<-meds[meds$ENCNTR_ID %in% dem$ENCNTR_ID,]
abx<-
meds[grepl('sulbactam', meds$NAME, ignore.case = T) | grepl('piperac
illin', meds$NAME, ignore.case = T),]
abx$admin_date<-
sapply(strsplit(abx$PERFRMD_FROM_DT_TM, ' '), '[',1)
abx$admin_date<-as.Date(abx$admin_date, format = '%d-%b-%y')

dem$tx_index<-NA
dem$tx_end<-NA
dem$DOT<-NA

abx2<-select(abx, ENCNTR_ID, admin_date)
abx2<-unique(abx2)

for(i in 1:nrow(dem)){                               ##~1.2
  hrs to complete
  dem$tx_index[i] = min(abx2$admin_date[abx2$ENCNTR_ID == dem$ENCNTR
_ID[i]])
  dem$tx_end[i] = max(abx2$admin_date[abx2$ENCNTR_ID == dem$ENCNTR_I
D[i]])
  dem$DOT[i]<-
length(unique(abx2$admin_date[abx2$ENCNTR_ID == dem$ENCNTR_ID[i]]))
}

dem$tx_index<-as.Date(dem$tx_index, origin='1970-01-01')
dem$tx_end<-as.Date(dem$tx_end, origin='1970-01-01')

dem<-dem[dem$DOT>=2,]

```

```

dem$caucasian[dem$RACE_CD_DES=='WHITE']<-1
dem$caucasian[is.na(dem$caucasian)]<-0

dem$ad_year<-sapply(strsplit(as.character(dem$ad_date), '-'), '[', 1)
dem<-dem[dem$GENDR_CD_DES !='UNKNOWN',]
#####
#####
##                                labs                                ##
#####
#####
labs<-
fread('///file2/crutter/UKHC - Cotner, Sarah - 2016/Cotner/labs.txt',
      sep='\t',header=T, colClasses='character')
labs<-labs[labs$ENCNTR_ID %in% dem$ENCNTR_ID]
scr<-labs[labs$ITM_NM =='Creatinine Level',]
scr$date<-as.POSIXct(scr$ENTRD_DT_TM, format='%d-%b-%y %H:%M:%S')
scr$VAL_NUM<-as.numeric(scr$VAL_NUM)
scr<-scr[!is.na(scr$VAL_NUM),]

dem<-dem[dem$ENCNTR_ID %in% scr$ENCNTR_ID,]
for(i in 1:nrow(dem)){
  x<- scr[scr$ENCNTR_ID == dem$ENCNTR_ID[i],]
  dem$baseline_scr[i]<-x$VAL_NUM[x$date==min(x$date)]
  dem$baseline_scr_date[i]<-min(x$date)}

dem$baseline_crcl<-(140-dem$AGE)/dem$baseline_scr
dem$baseline_crcl[dem$GENDR_CD_DES=='FEMALE']<-
dem$baseline_crcl[dem$GENDR_CD_DES=='FEMALE']*0.85

dem<-dem[!is.na(dem$baseline_scr),]
dem<-dem[dem$baseline_crcl>=30,]
crclcut<-
mean(dem$baseline_crcl, na.rm = T)+4*sd(dem$baseline_crcl)
dem<-dem[dem$baseline_crcl<=crclcut,]

scr$date2<-sapply(strsplit(as.character(scr$date), ' '), '[', 1)
scr$date2<-as.Date(scr$date2)

for(i in 1:nrow(dem)){
  x<- scr[scr$ENCNTR_ID == dem$ENCNTR_ID[i] & scr$date2 >= dem$tx_in
dex[i]+2 & scr$date2<dem$tx_end[i]+7,]
  dem$max_scr[i]<-max(x$VAL_NUM)[1]
  dem$max_scr_date[i]<-x$date2[x$VAL_NUM==max(x$VAL_NUM)][1]
}

```

```

dem$min_crcl<-(140-dem$AGE)/dem$max_scr
dem$min_crcl[dem$GENDR_CD_DES=='FEMALE']<-
dem$min_crcl[dem$GENDR_CD_DES=='FEMALE']*0.85
dem$percent_change<-(dem$min_crcl/dem$baseline_crcl-1)*100
dem<-dem[!is.infinite(dem$max_scr),]

dem$RIFLE[dem$percent_change <= -25 & dem$percent_change >-50]<-
'risk'
dem$RIFLE[dem$percent_change <= -50 & dem$percent_change >-75]<-
'injury'
dem$RIFLE[dem$percent_change <= -75| dem$max_scr>4]<- 'failure'

dem$aki[is.na(dem$RIFLE)]<-0
dem$aki[!is.na(dem$RIFLE)]<-1

dem$baseline_crcl_cat[dem$baseline_crcl <60]<-1
dem$baseline_crcl_cat[dem$baseline_crcl >=60 & dem$baseline_crcl<90]
<-2
dem$baseline_crcl_cat[dem$baseline_crcl >=90]<-3

#####
#####
##                               Nephrotoxin info                               ##
#####
#####
library(stringr)
neph<-
read.csv('//file2/crutter/UKHC - Cotner, Sarah - 2016/Cotner/COTNER_
NEPHROTOXIN.csv', colClasses='character')

vid<-
unique(meds$ENCNTR_ID[grepl('vancomycin', meds$NAME, ignore.case = T
)])
dem<- dem[!(dem$ENCNTR_ID %in% vid),]

ag<-
meds[grepl('aminogly', meds$THERPUTC_CATGRY, ignore.case = T),]
ag<-ag[!grepl('inhal', ag$NAME, ignore.case = T),]
ag<-ag[!grepl('irrigat', ag$NAME, ignore.case = T),]
ag$NAME<-gsub('zzz', '', ag$NAME)
ag$NAME<-gsub('inj', '', ag$NAME, ignore.case = T)
ag$NAME<-gsub('\\.', '', ag$NAME)
ag$NAME<-gsub('-', '', ag$NAME)
ag$NAME<-gsub('\\(pediatric\\)', '', ag$NAME, ignore.case = T)
ag$NAME<-str_trim(ag$NAME)
ag$date<-sapply(strsplit(ag$PERFRMD_FROM_DT_TM, ' '), '[', 1)
ag$date<-as.Date(ag$date, format = '%d-%b-%y')

```



```

ag<-ag[!grepl('neomycin', ag$NAME, ignore.case = T),]

amphb<-meds[grepl('amphote', meds$NAME, ignore.case = T),]
amphb<-amphb[!grepl('inhal', amphb$NAME, ignore.case = T),]
amphb<-amphb[!grepl('irrigat', amphb$NAME, ignore.case = T),]
amphb$NAME<-gsub('zzz', '', amphb$NAME)
amphb$NAME<-gsub('inj', '', amphb$NAME, ignore.case = T)
amphb$NAME<-gsub('\\.', '', amphb$NAME)
amphb$NAME<-gsub('-', '', amphb$NAME)
amphb$NAME<-gsub('\\(pediatric\\)', '', amphb$NAME, ignore.case = T)
amphb$NAME<-str_trim(amphb$NAME)
amphb$date<-sapply(strsplit(amphb$PERFRMD_FROM_DT_TM, ' '), '[', 1)
amphb$date<-as.Date(amphb$date, format = '%d-%b-%y')

cont<-neph[neph$NAME == '(ADM Override)',]
cont<-
cont[grepl('gado', cont$TASK_NM, ignore.case = T) | grepl('iodix', c
ont$TASK_NM, ignore.case = T)|
      grepl('iohex', cont$TASK_NM, ignore.case = T)| grepl('i
othal', cont$TASK_NM, ignore.case = T),]
cont<-cont[!grepl('oral', cont$TASK_NM, ignore.case = T),]
cont$date<-sapply(strsplit(cont$PERFRMD_FROM_DT_TM, ' '), '[', 1)
cont$date<-as.Date(cont$date)#, format = '%d-%b-%y')
cont<-cont[!is.na(cont$date),]

nsaids<-
meds[grepl('ibuprofen', meds$NAME, ignore.case=T)|grepl('naproxen',
meds$NAME, ignore.case=T)|
      grepl('indomethacin', meds$NAME, ignore.case=T)|grepl
('ketorolac', meds$NAME, ignore.case=T)|
      grepl('meloxicam', meds$NAME, ignore.case=T)|grepl('c
elecoxib', meds$NAME, ignore.case=T)|
      grepl('diclofenac', meds$NAME, ignore.case=T)|grepl('
etodolac', meds$NAME, ignore.case=T)|
      grepl('nabumetone', meds$NAME, ignore.case=T)|grepl('
piroxicam', meds$NAME, ignore.case=T)|
      grepl('sulindac', meds$NAME, ignore.case=T),]
nsaids$date<-
sapply(strsplit(nsaids$PERFRMD_FROM_DT_TM, ' '), '[', 1)
nsaids$date<-as.Date(nsaids$date, format = '%d-%b-%y')

#Need to follow up with Andrew
calc<-neph[neph$DRUG_KEY %in% c('d03752', 'd00079'),]
calc$date<-sapply(strsplit(calc$PERFRMD_FROM_DT_TM, ' '), '[', 1)
calc$date<-as.Date(calc$date)#, format = '%d-%b-%y')
calc<-calc[!is.na(calc$date),]

```

```

loop<-
meds[grepl('furosemide', meds$NAME, ignore.case=T)|grepl('bumetanide
', meds$NAME, ignore.case=T)|
      grepl('torsemide', meds$NAME, ignore.case=T)|grepl('eth
acryn', meds$NAME, ignore.case=T),]
loop$date<-sapply(strsplit(loop$PERFRMD_FROM_DT_TM, ' '), '[' ,1)
loop$date<-as.Date(loop$date, format = '%d-%b-%y')

vaso<-
meds[grepl('norepinephrine', meds$NAME, ignore.case=T)|grepl('epinep
hrine', meds$NAME, ignore.case=T)|
      grepl('phenylephrine', meds$NAME, ignore.case=T)|grepl(
'vasopressin', meds$NAME, ignore.case=T)|
      grepl('dopamine', meds$NAME, ignore.case=T),]
vaso$date<-sapply(strsplit(vaso$PERFRMD_FROM_DT_TM, ' '), '[' ,1)
vaso$date<-as.Date(vaso$date, format = '%d-%b-%y')

iono<-
meds[grepl('Dobutamine', meds$NAME, ignore.case=T)|grepl('milrinone'
, meds$NAME, ignore.case=T),]
iono$date<-sapply(strsplit(iono$PERFRMD_FROM_DT_TM, ' '), '[' ,1)
iono$date<-as.Date(iono$date, format = '%d-%b-%y')

acei<-neph[grepl('pril', neph$NAME, ignore.case=T),]
acei$date<-sapply(strsplit(acei$PERFRMD_FROM_DT_TM, ' '), '[' ,1)
acei$date<-as.Date(acei$date)#, format = '%d-%b-%y')
acei<-acei[complete.cases(acei),]

# NEed to follow up with Andrew
arb<-
neph[neph$DRUG_KEY %in% c('d03821', 'd04322', 'd04113', 'd04222', 'd043
64', 'd04801'),]
arb$date<-sapply(strsplit(arb$PERFRMD_FROM_DT_TM, ' '), '[' ,1)
arb$date<-as.Date(arb$date)#, format = '%m/%d/%Y')
arb<-arb[!is.na(arb$date),]

for(i in 1:nrow(dem)){
  if(!(dem$ENCNTR_ID [i] %in% ag$ENCNTR_ID)){
    dem$aminoglycoside_exp[i]<-0
    next
  }
  else{
    x<-ag[ag$ENCNTR_ID == dem$ENCNTR_ID[i],]
    x<-x[dplyr::between(x = x$date, left = dem$tx_index[i]-
1, right = dem$tx_end[i]),]
    if(dim(x)[1]>0){
      dem$aminoglycoside_exp[i]<-1
    }
    else{

```

```

    dem$aminoglycoside_exp[i]<-0
  }
}

for(i in 1:nrow(dem)){
  if(!(dem$ENCNTR_ID [i] %in% amphb$ENCNTR_ID)){
    dem$amphb_exp[i]<-0
    next
  }
  else{
    x<-amphb[amphb$ENCNTR_ID == dem$ENCNTR_ID[i],]
    x<-x[dplyr::between(x = x$date, left = dem$tx_index[i]-
1, right = dem$tx_end[i]),]
    if(dim(x)[1]>0){
      dem$amphb_exp[i]<-1
    }
    else{
      dem$amphb_exp[i]<-0
    }
  }
}

for(i in 1:nrow(dem)){
  if(!(dem$ENCNTR_ID [i] %in% cont$ENCNTR_ID)){
    dem$cont_exp[i]<-0
    next
  }
  else{
    x<-cont[cont$ENCNTR_ID == dem$ENCNTR_ID[i],]
    x<-x[dplyr::between(x = x$date, left = dem$tx_index[i]-
1, right = dem$tx_end[i]#
),]
    if(dim(x)[1]>0){
      dem$cont_exp[i]<-1
    }
    else{
      dem$cont_exp[i]<-0
    }
  }
}

for(i in 1:nrow(dem)){
  if(!(dem$ENCNTR_ID [i] %in% nsaid$ENCNTR_ID)){
    dem$nsaid_exp[i]<-0
    next
  }
  else{
    x<-nsaid[nsaid$ENCNTR_ID == dem$ENCNTR_ID[i],]

```

```

    x<-x[dplyr::between(x = x$date, left = dem$tx_index[i]-
1, right = dem$tx_end[i]),]
    if(dim(x)[1]>0){
        dem$nsaids_exp[i]<-1
    }
    else{
        dem$nsaids_exp[i]<-0
    }
}
}

for(i in 1:nrow(dem)){
    if(!(dem$ENCNTR_ID [i] %in% calc$ENCNTR_ID)){
        dem$calc_exp[i]<-0
        next
    }
    else{
        x<-calc[calc$ENCNTR_ID == dem$ENCNTR_ID[i],]
        x<-x[dplyr::between(x = x$date, left = dem$tx_index[i]-
1, right = dem$tx_end[i]#
),]
        if(dim(x)[1]>0){
            dem$calc_exp[i]<-1
        }
        else{
            dem$calc_exp[i]<-0
        }
    }
}

for(i in 1:nrow(dem)){
    if(!(dem$ENCNTR_ID [i] %in% loop$ENCNTR_ID)){
        dem$loop_exp[i]<-0
        next
    }
    else{
        x<-loop[loop$ENCNTR_ID == dem$ENCNTR_ID[i],]
        x<-x[dplyr::between(x = x$date, left = dem$tx_index[i]-
1, right = dem$tx_end[i]),]
        if(dim(x)[1]>0){
            dem$loop_exp[i]<-1
        }
        else{
            dem$loop_exp[i]<-0
        }
    }
}

for(i in 1:nrow(dem)){

```

```

if(!(dem$ENCNTR_ID [i] %in% vaso$ENCNTR_ID)){
  dem$vaso_exp[i]<-0
  next
}
else{
  x<-vaso[vaso$ENCNTR_ID == dem$ENCNTR_ID[i],]
  x<-x[dplyr::between(x = x$date, left = dem$tx_index[i]-
1, right = dem$tx_end[i]),]
  if(dim(x)[1]>0){
    dem$vaso_exp[i]<-1
  }
  else{
    dem$vaso_exp[i]<-0
  }
}
}

for(i in 1:nrow(dem)){
  if(!(dem$ENCNTR_ID [i] %in% iono$ENCNTR_ID)){
    dem$iono_exp[i]<-0
    next
  }
  else{
    x<-iono[iono$ENCNTR_ID == dem$ENCNTR_ID[i],]
    x<-x[dplyr::between(x = x$date, left = dem$tx_index[i]-
1, right = dem$tx_end[i]),]
    if(dim(x)[1]>0){
      dem$iono_exp[i]<-1
    }
    else{
      dem$iono_exp[i]<-0
    }
  }
}

for(i in 1:nrow(dem)){
  if(!(dem$ENCNTR_ID [i] %in% acei$ENCNTR_ID)){
    dem$acei_exp[i]<-0
    next
  }
  else{
    x<-acei[acei$ENCNTR_ID == dem$ENCNTR_ID[i],]
    x<-x[dplyr::between(x = x$date, left = dem$tx_index[i]-
1, right = dem$tx_end[i]),]
    if(dim(x)[1]>0){
      dem$acei_exp[i]<-1
    }
    else{
      dem$acei_exp[i]<-0
    }
  }
}

```

```

    }
  }
}

for(i in 1:nrow(dem)){
  if(!(dem$ENCNTR_ID [i] %in% arb$ENCNTR_ID)){
    dem$arb_exp[i]<-0
    next
  }
  else{
    x<-arb[arb$ENCNTR_ID == dem$ENCNTR_ID[i],]
    x<-x[dplyr::between(x = x$date, left = dem$tx_index[i]-
1, right = dem$tx_end[i]#
),]
    if(dim(x)[1]>0){
      dem$arb_exp[i]<-1
    }
    else{
      dem$arb_exp[i]<-0
    }
  }
}

rm(ag, amphb, cont, nsaid, calc, loop, vaso, iono, acei, arb)
#####
#####
##                               Vital signs clean up
##
#####
#####
vit<-
fread('///file2/crutter/UKHC - Cotner, Sarah - 2016/Cotner/cotner_vit
als.csv', sep=',', colClasses='character')
vit<-vit[vit$ENCNTR_ID %in% dem$ENCNTR_ID,]
bp<-
vit[grepl('Systolic', vit$LEFT_LABEL, ignore.case = T)| grepl('diast
olic', vit$LEFT_LABEL, ignore.case = T),]
bp$VAL_TXT<-as.numeric(bp$VAL_TXT)

bpcast<-
dcast.data.table(ENCNTR_ID+RECRD_DT_TM~LEFT_LABEL, value.var = 'VAL_
TXT', data=bp, fun.aggregate = min)
bpcast$dbp[is.infinite(bpcast$'Direct Arterial Blood Pressure (Diast
olic)')<-bpcast$Diastolic
bpcast$sbp[is.infinite(bpcast$'Direct Arterial Blood Pressure (Systo
lic)')<-bpcast$Systolic
bpcast$dbp[is.infinite(bpcast$Diastolic)]<-
bpcast$'Direct Arterial Blood Pressure (Diastolic)']

```

```

bpcast$sbp[is.infinite(bpcast$Systolic)]<-
bpcast$'Direct Arterial Blood Pressure (Systolic)'
bpcast$dbp[is.infinite(bpcast$'Direct Arterial Blood Pressure (Diast
olic)')& is.infinite(bpcast$Diastolic)]<-NA
bpcast$sbp[is.infinite(bpcast$'Direct Arterial Blood Pressure (Systo
lic)')& is.infinite(bpcast$Systolic)]<-NA
bpcast$dbp[is.infinite(bpcast$dbp)]<-NA
bpcast$sbp[is.infinite(bpcast$sbp)]<-NA
bp<-dplyr::select(bpcast, ENCNTN_ID, RECRD_DT_TM, dbp, sbp)

bp<-bp[complete.cases(bp),]
bp$date<-sapply(strsplit(bp$RECRD_DT_TM, ' '), '[',1)
bp$date<-as.Date(bp$date, format = '%d-%b-%y')
bp$RECRD_DT_TM<-as.POSIXct(bp$RECRD_DT_TM, format='%d-%b-
%y %H:%M:%S')

bp$map<-round((2*bp$dbp +bp$sbp)/3,2)
sbpcut<-mean(bp$sbp)+4*sd(bp$sbp)
dbpcut<-mean(bp$dbp)+4*sd(bp$dbp)
mapcut<-mean(bp$map)+4*sd(bp$map)
bp<-bp[bp$sbp<=sbpcut & bp$dbp <= dbpcut & bp$map<=mapcut,]

dem$hypotension<-0

for(i in 1:nrow(dem)){
  if(min(bp$map[bp$ENCNTN_ID == dem$ENCNTN_ID[i] & dplyr::between(bp
$date,
                                                                    le
ft = dem$tx_index[i]-1,
                                                                    ri
ght = dem$tx_end[i]]))<65){
    dem$hypotension[i]<-1
    next
  }
  if(min(sbp<-
bp$sbp[bp$ENCNTN_ID == dem$ENCNTN_ID[i] & dplyr::between(bp$date,

left = dem$tx_index[i]-1,

right = dem$tx_end[i]]))<90){
    dem$hypotension[i]<-1
    next
  }
  if(dem$vaso_exp[i]==1){
    dem$hypotension[i]<-1
  }
}

rm(bp, bpcast, vit)

```

Matching

```
library(dplyr)
library(MatchIt)
library(data.table)
mat<-
dplyr::select(dem, ENCNTR_ID, age_group, GENDR_CD_DES, COMORBIDITY_S
CORE, baseline_crcl_cat, hypotension, drug)

mat$drug[mat$drug=='AS']<-1
mat$drug[mat$drug=='PTZ']<-0

mdf<-
matchit(drug~age_group+ GENDR_CD_DES+ COMORBIDITY_SCORE+ baseline_cr
cl_cat+ hypotension,
        data=mat, ratio =3, exact = c('GENDR_CD_DES', 'age_group
'))

summary(mdf)
m.out<-match.data(mdf)
matdem<-dem[dem$ENCNTR_ID %in% m.out$ENCNTR_ID,]
```

Modeling

```
mat<-matdem
mat$aki<-as.numeric(mat$aki)
attach(mat)
x<- 'binomial'
library(sjPlot)
age<-glm(aki~factor(age_group), family=x, data=mat)
sjt.glm(age)

sex<-glm(aki~factor(GENDR_CD_DES), x, mat)
sjt.glm(sex)
race<-glm(aki~factor(caucasian), x, mat)
sjt.glm(race)
cci<-glm(aki~as.numeric(COMORBIDITY_SCORE), x, mat)
sjt.glm(cci)
crcl<-glm(aki~factor(baseline_crcl_cat), x, mat)
sjt.glm(crcl)
ag<-glm(aki~aminoglycoside_exp,x, mat)
sjt.glm(ag)
ab<-glm(aki~amphb_exp,x,mat)
sjt.glm(ab)
ac<-glm(aki~acei_exp, x, mat)
```



```

sjt.glm(ac)
loop<-glm(aki~loop_exp,x, mat)
sjt.glm(loop)
ns<-glm(aki~nsaids_exp, x, mat)
sjt.glm(ns)
van<-glm(aki~vanc_exp, x, mat)
sjt.glm(van)
vas<-glm(aki~vaso_exp, x, mat)
sjt.glm(vas)
cf<-glm(aki~CF, x, mat)
sjt.glm(cf)
dm<-glm(aki~dm, x, mat)
sjt.glm(dm)
htn<-glm(aki~HTN,x,mat)
sjt.glm(htn)
hf<-glm(aki~hf, x, mat)
sjt.glm(hf)
icu<-glm(aki~icu_admit, x, mat)
sjt.glm(icu)
drug<-glm(aki~factor(drug), x, mat)
sjt.glm(drug)
hy<-glm(aki~hypotension, x, mat)
sjt.glm(hy)
pi<-glm(aki~group, x, mat)
sjt.glm(pi)

detach(mat)
attach(mat)
arb<-glm(aki~arb_exp, x, mat)
sjt.glm(arb)
cont<-glm(aki~cont_exp,x,mat)
sjt.glm(cont)
calc<-glm(aki~calc_exp, x,mat)
sjt.glm(calc)

mod<-
glm(aki~drug+GENDR_CD_DES+aminoglycoside_exp+amphb_exp+acei_exp+calc_
_exp+cont_exp+loop_exp+vaso_exp+dm+hf+nsaids_exp
      , x, mat)
sjt.glm(mod, showAIC = T)

modstep<-step(mod)

mod2<-
glm(formula = aki ~ drug+ GENDR_CD_DES + aminoglycoside_exp + amphb_
_exp +
      calc_exp + cont_exp + loop_exp, family = x, data = mat)
sjt.glm(mod2, showAIC = T)

```

```

library(ResourceSelection)
hoslem.test(mod2$y, fitted(mod2), g = 100)
hoslem.test(mod$y, fitted(mod), g = 100)

library(rms)
mod1rm<-
lrm(aki~group+age_group+GENDR_CD_DES+as.numeric(COMORBIDITY_SCORE)+b
aseline_crcl_cat+aminoglycoside_exp+
      amphb_exp+acei_exp+calc_exp+loop_exp+nsaids_exp+vanc_e
xp+vaso_exp+CF+dm+HTN+hf+icu_admit+drug+hypotension, data = mat)
mod21rm<-
lrm(formula = aki ~ group + age_group + as.numeric(COMORBIDITY_SCORE
) +
      baseline_crcl_cat + aminoglycoside_exp + amphb_exp +
calc_exp +
      loop_exp + nsaids_exp + vanc_exp + vaso_exp + CF + dm
+ hf +
      drug + hypotension, data = mat)

mod2i<-
glm(formula = aki ~ group + age_group + as.numeric(COMORBIDITY_SCORE
) +
      baseline_crcl_cat + aminoglycoside_exp + amphb_exp + ca
lc_exp +
      loop_exp + nsaids_exp + vanc_exp + vaso_exp + CF + dm +
hf +
      drug*vanc_exp + hypotension, family = x, data = mat)

```

Data table generation

```

restab<-data.frame(variable = rep(NA,100), AS= NA, PTZ = NA, p=NA)
restab$variable[1] = 'N'
restab$AS[1] = paste(nrow(dem[dem$drug=='AS',]), " (", (round(nrow(d
em[dem$drug=='AS',])/nrow(dem),3)*100),'%')', sep='')
restab$PTZ[1] = paste(nrow(dem[dem$drug=='PTZ',]), " (", (round(nrow
(dem[dem$drug=='PTZ',])/nrow(dem),3)*100),'%')', sep='')

attach(dem)

restab$variable[2]<- 'Age (mean[SD])'
restab$AS[2]<-
paste(round(mean(AGE[drug=='AS'], na.rm = T),2), ' (', round(sd(AGE[
drug=='AS'], na.rm = T),2), ')', sep='')

```

```

restab$PTZ[2]<-
paste(round(mean(AGE[drug=='PTZ'], na.rm = T),2), ' (', round(sd(AGE
[drug=='PTZ'], na.rm = T),2), ')', sep='')
restab$p[2]<-t.test(AGE~drug)$p.value

restab$variable[3]<-'Age (median [IQR])'
restab$AS[3]<-
paste(median(AGE[drug=='AS'], na.rm=T), " (", quantile(AGE[drug=='AS
'], probs=0.25, na.rm = T), '- ',
      quantile(AGE[drug=='AS'], probs=0.75, na.rm = T)
,')', sep='')
restab$PTZ[3]<-
paste(median(AGE[drug=='PTZ'], na.rm=T), " (", quantile(AGE[drug=='P
TZ'], probs=0.25, na.rm = T), '- ',
      quantile(AGE[drug=='PTZ'], probs=0.75, na.rm
= T), ')', sep='')
restab$p[3]<-wilcox.test(AGE~drug)$p.value

restab$variable[4]<-'Gender'
restab$variable[5]<-'Male'
restab$AS[5]<-
paste(nrow(dem[dem$GENDR_CD_DES=='MALE' & dem$drug=='AS',]), ' (',
      round((nrow(dem[dem$GENDR_CD_DES=='MALE' & dem$d
rug=='AS',])/nrow(dem[dem$drug=='AS',])*100),2), '%)', sep='')
restab$PTZ[5]<-
paste(nrow(dem[dem$GENDR_CD_DES=='MALE' & dem$drug=='PTZ',]), ' (',
      round((nrow(dem[dem$GENDR_CD_DES=='MALE' & de
m$drug=='PTZ',])/nrow(dem[dem$drug=='PTZ',])*100),2), '%)', sep='')

restab$variable[6]<-'Female'
restab$AS[6]<-
paste(nrow(dem[dem$GENDR_CD_DES=='FEMALE' & dem$drug=='AS',]), ' (',
      round((nrow(dem[dem$GENDR_CD_DES=='FEMALE' & dem
$drug=='AS',])/nrow(dem[dem$drug=='AS',])*100),2), '%)', sep='')
restab$PTZ[6]<-
paste(nrow(dem[dem$GENDR_CD_DES=='FEMALE' & dem$drug=='PTZ',]), ' ( '
,
      round((nrow(dem[dem$GENDR_CD_DES=='FEMALE' &
dem$drug=='PTZ',])/nrow(dem[dem$drug=='PTZ',])*100),2), '%)', sep=''
)
restab$p[4]<-chisq.test(table(GENDR_CD_DES, drug))$p.value

restab$variable[7]<-'caucasian'
restab$AS[7]<-
paste(nrow(dem[dem$caucasian==1 & dem$drug=='AS',]), ' (',

```

```

round((nrow(dem[dem$caucasian==1 & dem$drug=='AS
',])/nrow(dem[dem$drug=='AS',])*100),2), '%', sep='')
restab$PTZ[7]<-
paste(nrow(dem[dem$caucasian==1 & dem$drug=='PTZ',]), ' (',
round((nrow(dem[dem$caucasian==1 & dem$drug=='
'PTZ',])/nrow(dem[dem$drug=='PTZ',])*100),2), '%', sep='')
restab$p[7]<-chisq.test(table(caucasian, drug))$p.value

restab$variable[8]<- 'WT (mean[SD])'
restab$AS[8]<-
paste(round(mean(INIT_WT[drug=='AS'], na.rm = T),2), ' (', round(sd(
INIT_WT[drug=='AS'], na.rm = T),2), ')', sep='')
restab$PTZ[8]<-
paste(round(mean(INIT_WT[drug=='PTZ'], na.rm = T),2), ' (', round(sd
(INIT_WT[drug=='PTZ'], na.rm = T),2), ')', sep='')
restab$p[8]<-t.test(INIT_WT~drug)$p.value

restab$variable[9]<- 'WT (median [IQR])'
restab$AS[9]<-
paste(median(INIT_WT[drug=='AS'], na.rm=T), " (", quantile(INIT_WT[d
rug=='AS'], probs=0.25, na.rm = T), '- ',
quantile(INIT_WT[drug=='AS'], probs=0.75, na.rm
= T), ')', sep='')
restab$PTZ[9]<-
paste(median(INIT_WT[drug=='PTZ'], na.rm=T), " (", quantile(INIT_WT[
drug=='PTZ'], probs=0.25, na.rm = T), '- ',
quantile(INIT_WT[drug=='PTZ'], probs=0.75, na
.rm = T), ')', sep='')
restab$p[9]<-wilcox.test(INIT_WT~drug)$p.value

restab$variable[10]<- 'BMI (mean[SD])'
restab$AS[10]<-
paste(round(mean(BMI[drug=='AS'], na.rm = T),2), ' (', round(sd(BMI[
drug=='AS'], na.rm = T),2), ')', sep='')
restab$PTZ[10]<-
paste(round(mean(BMI[drug=='PTZ'], na.rm = T),2), ' (', round(sd(BMI
[drug=='PTZ'], na.rm = T),2), ')', sep='')
restab$p[10]<-t.test(BMI~drug)$p.value

restab$variable[11]<- 'BMI (median [IQR])'
restab$AS[11]<-
paste(round(median(BMI[drug=='AS'], na.rm=T),2), " (", round(quantil
e(BMI[drug=='AS'], probs=0.25, na.rm = T),2), '- ',
round(quantile(BMI[drug=='AS'], probs=0.75, na.
rm = T),2), ')', sep='')
restab$PTZ[11]<-
paste(round(median(BMI[drug=='PTZ'], na.rm=T),2), " (", round(quantil
e(BMI[drug=='PTZ'], probs=0.25, na.rm = T),2), '- ',

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round(quantile(BMI[drug=='PTZ'], probs=0.75,
na.rm = T),2),')', sep='')
restab$p[11]<-wilcox.test(BMI~drug)$p.value

restab$variable[12]<-'COMORBIDITY_SCORE (mean[SD])'
restab$AS[12]<-
paste(round(mean(dem$COMORBIDITY_SCORE[drug=='AS'], na.rm = T),2), '
(', round(sd(dem$COMORBIDITY_SCORE[drug=='AS'], na.rm = T),2),')',
sep='')
restab$PTZ[12]<-
paste(round(mean(dem$COMORBIDITY_SCORE[drug=='PTZ'], na.rm = T),2),
'(', round(sd(dem$COMORBIDITY_SCORE[drug=='PTZ'], na.rm = T),2),')'
, sep='')
restab$p[12]<-t.test(dem$COMORBIDITY_SCORE~drug)$p.value

restab$variable[13]<-'COMORBIDITY_SCORE (median [IQR])'
restab$AS[13]<-
paste(median(dem$COMORBIDITY_SCORE[drug=='AS'], na.rm=T), "(", quan
tile(dem$COMORBIDITY_SCORE[drug=='AS'], probs=0.25, na.rm = T), '-
',
round(quantile(dem$COMORBIDITY_SCORE[drug=='AS'], pro
bs=0.75, na.rm = T),')', sep='')
restab$PTZ[13]<-
paste(median(dem$COMORBIDITY_SCORE[drug=='PTZ'], na.rm=T), "(", qua
ntile(dem$COMORBIDITY_SCORE[drug=='PTZ'], probs=0.25, na.rm = T), '-
',
round(quantile(dem$COMORBIDITY_SCORE[drug=='PTZ'],
probs=0.75, na.rm = T),')', sep='')
restab$p[13]<-wilcox.test(dem$COMORBIDITY_SCORE~drug)$p.value

restab$variable[14]<-'baseline crcl (mean[SD])'
restab$AS[14]<-
paste(round(mean(dem$baseline_crcl[drug=='AS'], na.rm = T),2), '(',
round(sd(dem$baseline_crcl[drug=='AS'], na.rm = T),2),')', sep='')

restab$PTZ[14]<-
paste(round(mean(dem$baseline_crcl[drug=='PTZ'], na.rm = T),2), ' ('
, round(sd(dem$baseline_crcl[drug=='PTZ'], na.rm = T),2),')', sep='')
)
restab$p[14]<-t.test(dem$baseline_crcl~drug)$p.value

restab$variable[15]<-'baseline crcl (median [IQR])'
restab$AS[15]<-
paste(round(median(dem$baseline_crcl[drug=='AS'], na.rm=T),2), "(",
round(quantile(dem$baseline_crcl[drug=='AS'], p
robs=0.25, na.rm = T),2),'- ',
round(quantile(dem$baseline_crcl[drug=='AS'], p
robs=0.75, na.rm = T),2),')', sep='')

```

```

restab$PTZ[15]<-
paste(round(median(dem$baseline_crcl[drug=='PTZ'], na.rm=T),2), " ("
,
      round(quantile(dem$baseline_crcl[drug=='PTZ'
], probs=0.25, na.rm = T),2), '- ',
      round(quantile(dem$baseline_crcl[drug=='PTZ'
], probs=0.75, na.rm = T),2), ')', sep='')
restab$p[15]<-wilcox.test(dem$baseline_crcl~drug)$p.value

restab$variable[16]<- 'baseline crcl drug'
restab$variable[17]<- '30-59 mL/min'
restab$AS[17]<-
paste(nrow(dem[dem$baseline_crcl_cat == 1 & dem$drug=='AS',]), ' ('
,
      round((nrow(dem[dem$baseline_crcl_cat == 1 & de
m$drug=='AS', ])/nrow(dem[dem$drug=='AS', ])*100),2), '%)', sep='')
restab$PTZ[17]<-
paste(nrow(dem[dem$baseline_crcl_cat == 1 & dem$drug=='PTZ',]), ' ('
,
      round((nrow(dem[dem$baseline_crcl_cat == 1 &
dem$drug=='PTZ', ])/nrow(dem[dem$drug=='PTZ', ])*100),2), '%)', sep=
')')
restab$variable[18]<- '60-89 mL/min'
restab$AS[18]<-
paste(nrow(dem[dem$baseline_crcl_cat == 2 & dem$drug=='AS',]), ' ('
,
      round((nrow(dem[dem$baseline_crcl_cat == 2 & de
m$drug=='AS', ])/nrow(dem[dem$drug=='AS', ])*100),2), '%)', sep='')
restab$PTZ[18]<-
paste(nrow(dem[dem$baseline_crcl_cat == 2 & dem$drug=='PTZ',]), ' ('
,
      round((nrow(dem[dem$baseline_crcl_cat == 2 &
dem$drug=='PTZ', ])/nrow(dem[dem$drug=='PTZ', ])*100),2), '%)', sep=
')')
restab$variable[19]<- '>=90 mL/min'
restab$AS[19]<-
paste(nrow(dem[dem$baseline_crcl_cat == 3 & dem$drug=='AS',]), ' ('
,
      round((nrow(dem[dem$baseline_crcl_cat == 3 & de
m$drug=='AS', ])/nrow(dem[dem$drug=='AS', ])*100),2), '%)', sep='')
restab$PTZ[19]<-
paste(nrow(dem[dem$baseline_crcl_cat == 3 & dem$drug=='PTZ',]), ' ('
,
      round((nrow(dem[dem$baseline_crcl_cat == 3 &
dem$drug=='PTZ', ])/nrow(dem[dem$drug=='PTZ', ])*100),2), '%)', sep=
')')
restab$p[16]<-chisq.test(table(baseline_crcl_cat, drug))$p.value

restab$variable[20]<- 'Concomitant nephrotoxins'

```

```

restab$variable[21]<- 'Aminoglycosides'
restab$AS[21]<-
paste(nrow(dem[dem$aminoglycoside_exp == 1 & dem$drug=='AS',]), ' (',
      round((nrow(dem[dem$aminoglycoside_exp == 1 & dem$drug=='AS',])/nrow(dem[dem$drug=='AS',])*100),2),
      '%)', sep='')
restab$PTZ[21]<-
paste(nrow(dem[dem$aminoglycoside_exp == 1 & dem$drug=='PTZ',]), ' (',
      round((nrow(dem[dem$aminoglycoside_exp == 1 & dem$drug=='PTZ',])/nrow(dem[dem$drug=='PTZ',])*100),2),
      '%)', sep='')
restab$p[21]<-chisq.test(table(aminoglycoside_exp, drug))$p.value

restab$variable[22]<- 'amphb'
restab$AS[22]<-
paste(nrow(dem[dem$amphb_exp == 1 & dem$drug=='AS',]), ' (',
      round((nrow(dem[dem$amphb_exp == 1 & dem$drug=='AS',])/nrow(dem[dem$drug=='AS',])*100),2),
      '%)', sep='')
restab$PTZ[22]<-
paste(nrow(dem[dem$amphb_exp == 1 & dem$drug=='PTZ',]), ' (',
      round((nrow(dem[dem$amphb_exp == 1 & dem$drug=='PTZ',])/nrow(dem[dem$drug=='PTZ',])*100),2),
      '%)', sep='')
restab$p[22]<-chisq.test(table(amphb_exp, drug))$p.value

restab$variable[23]<- 'acei'
restab$AS[23]<-
paste(nrow(dem[dem$acei_exp == 1 & dem$drug=='AS',]), ' (',
      round((nrow(dem[dem$acei_exp == 1 & dem$drug=='AS',])/nrow(dem[dem$drug=='AS',])*100),2),
      '%)', sep='')
restab$PTZ[23]<-
paste(nrow(dem[dem$acei_exp == 1 & dem$drug=='PTZ',]), ' (',
      round((nrow(dem[dem$acei_exp == 1 & dem$drug=='PTZ',])/nrow(dem[dem$drug=='PTZ',])*100),2),
      '%)', sep='')
restab$p[23]<-chisq.test(table(acei_exp, drug))$p.value

restab$variable[24]<- 'arb'
restab$AS[24]<-
paste(nrow(dem[dem$arb_exp == 1 & dem$drug=='AS',]), ' (',
      round((nrow(dem[dem$arb_exp == 1 & dem$drug=='AS',])/nrow(dem[dem$drug=='AS',])*100),2),
      '%)', sep='')
restab$PTZ[24]<-
paste(nrow(dem[dem$arb_exp == 1 & dem$drug=='PTZ',]), ' (',

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```

round((nrow(dem[dem$arb_exp == 1 & dem$drug=
='PTZ', ])/nrow(dem[dem$drug=='PTZ', ])*100),2),
      '%)', sep='')
restab$p[24]<-chisq.test(table(arb_exp, drug))$p.value

restab$variable[25]<- 'cont'
restab$AS[25]<-
paste(nrow(dem[dem$cont_exp == 1 & dem$drug=='AS', ]), ' (',
      round((nrow(dem[dem$cont_exp == 1 & dem$drug=='
AS', ])/nrow(dem[dem$drug=='AS', ])*100),2),
      '%)', sep='')
restab$PTZ[25]<-
paste(nrow(dem[dem$cont_exp == 1 & dem$drug=='PTZ', ]), ' (',
      round((nrow(dem[dem$cont_exp == 1 & dem$drug
=='PTZ', ])/nrow(dem[dem$drug=='PTZ', ])*100),2),
      '%)', sep='')
restab$p[25]<-chisq.test(table(cont_exp, drug))$p.value

restab$variable[26]<- 'loop'
restab$AS[26]<-
paste(nrow(dem[dem$loop_exp == 1 & dem$drug=='AS', ]), ' (',
      round((nrow(dem[dem$loop_exp == 1 & dem$drug=='
AS', ])/nrow(dem[dem$drug=='AS', ])*100),2),
      '%)', sep='')
restab$PTZ[26]<-
paste(nrow(dem[dem$loop_exp == 1 & dem$drug=='PTZ', ]), ' (',
      round((nrow(dem[dem$loop_exp == 1 & dem$drug
=='PTZ', ])/nrow(dem[dem$drug=='PTZ', ])*100),2),
      '%)', sep='')
restab$p[26]<-chisq.test(table(loop_exp, drug))$p.value

restab$variable[27]<- 'nsaids'
restab$AS[27]<-
paste(nrow(dem[dem$nsaids_exp == 1 & dem$drug=='AS', ]), ' (',
      round((nrow(dem[dem$nsaids_exp == 1 & dem$drug=
='AS', ])/nrow(dem[dem$drug=='AS', ])*100),2),
      '%)', sep='')
restab$PTZ[27]<-
paste(nrow(dem[dem$nsaids_exp == 1 & dem$drug=='PTZ', ]), ' (',
      round((nrow(dem[dem$nsaids_exp == 1 & dem$dr
ug=='PTZ', ])/nrow(dem[dem$drug=='PTZ', ])*100),2),
      '%)', sep='')
restab$p[27]<-chisq.test(table(nsaids_exp, drug))$p.value

restab$variable[28]<- 'calc'
restab$AS[28]<-
paste(nrow(dem[dem$calc_exp == 1 & dem$drug=='AS', ]), ' (',

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round((nrow(dem[dem$calc_exp == 1 & dem$drug=='
AS', ])/nrow(dem[dem$drug=='AS', ])*100),2),
      '%)', sep='')
restab$PTZ[28]<-
paste(nrow(dem[dem$calc_exp == 1 & dem$drug=='PTZ', ]), ' (',
      round((nrow(dem[dem$calc_exp == 1 & dem$drug
=='PTZ', ])/nrow(dem[dem$drug=='PTZ', ])*100),2),
      '%)', sep='')
restab$p[28]<-chisq.test(table(calc_exp, drug))$p.value

# restab$variable[29]<-'vanc'
# restab$AS[29]<-
paste(nrow(dem[dem$vanc_exp == 1 & dem$drug=='AS', ]), ' (',
#      round((nrow(dem[dem$vanc_exp == 1 & dem$drug=
=='AS', ])/nrow(dem[dem$drug=='AS', ])*100),2),
#      '%)', sep='')
# restab$PTZ[29]<-
paste(nrow(dem[dem$vanc_exp == 1 & dem$drug=='PTZ', ]), ' (',
#      round((nrow(dem[dem$vanc_exp == 1 & dem$dr
ug=='PTZ', ])/nrow(dem[dem$drug=='PTZ', ])*100),2),
#      '%)', sep='')
# restab$p[29]<-chisq.test(table(vanc_exp, drug))$p.value

restab$variable[30]<-'vaso'
restab$AS[30]<-
paste(nrow(dem[dem$vaso_exp == 1 & dem$drug=='AS', ]), ' (',
      round((nrow(dem[dem$vaso_exp == 1 & dem$drug=='
AS', ])/nrow(dem[dem$drug=='AS', ])*100),2),
      '%)', sep='')
restab$PTZ[30]<-
paste(nrow(dem[dem$vaso_exp == 1 & dem$drug=='PTZ', ]), ' (',
      round((nrow(dem[dem$vaso_exp == 1 & dem$drug
=='PTZ', ])/nrow(dem[dem$drug=='PTZ', ])*100),2),
      '%)', sep='')
restab$p[30]<-chisq.test(table(vaso_exp, drug))$p.value

restab$variable[31]<-'Comorbidities'
restab$variable[32]<-'DM'
restab$AS[32]<-
paste(nrow(dem[dem$dm==1 & dem$drug=='AS', ]), ' (',
      round((nrow(dem[dem$dm==1 & dem$drug=='AS', ])/n
row(dem[dem$drug=='AS', ])*100),2), '%)', sep='')
restab$PTZ[32]<-
paste(nrow(dem[dem$dm==1 & dem$drug=='PTZ', ]), ' (',
      round((nrow(dem[dem$dm==1 & dem$drug=='PTZ',
 ])/nrow(dem[dem$drug=='PTZ', ])*100),2), '%)', sep='')
restab$p[32]<-chisq.test(table(dem$dm, drug))$p.value

restab$variable[33]<-'HF'

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restab$AS[33]<-
paste(nrow(dem[dem$hf==1 & dem$drug=='AS',]), ' (',
      round((nrow(dem[dem$hf==1 & dem$drug=='AS',])/n
row(dem[dem$drug=='AS',])*100),2), '%)', sep='')
restab$PTZ[33]<-
paste(nrow(dem[dem$hf==1 & dem$drug=='PTZ',]), ' (',
      round((nrow(dem[dem$hf==1 & dem$drug=='PTZ',
])/nrow(dem[dem$drug=='PTZ',])*100),2), '%)', sep='')
restab$p[33]<-chisq.test(table(dem$hf, drug))$p.value

restab$variable[34]<- 'HTN'
restab$AS[34]<-
paste(nrow(dem[dem$HTN==1 & dem$drug=='AS',]), ' (',
      round((nrow(dem[dem$HTN==1 & dem$drug=='AS',])/
nrow(dem[dem$drug=='AS',])*100),2), '%)', sep='')
restab$PTZ[34]<-
paste(nrow(dem[dem$HTN==1 & dem$drug=='PTZ',]), ' (',
      round((nrow(dem[dem$HTN==1 & dem$drug=='PTZ',
])/nrow(dem[dem$drug=='PTZ',])*100),2), '%)', sep='')
restab$p[34]<-chisq.test(table(HTN, drug))$p.value

restab$variable[35]<- 'CF'
restab$AS[35]<-
paste(nrow(dem[dem$CF==1 & dem$drug=='AS',]), ' (',
      round((nrow(dem[dem$CF==1 & dem$drug=='AS',])/n
row(dem[dem$drug=='AS',])*100),2), '%)', sep='')
restab$PTZ[35]<-
paste(nrow(dem[dem$CF==1 & dem$drug=='PTZ',]), ' (',
      round((nrow(dem[dem$CF==1 & dem$drug=='PTZ',
])/nrow(dem[dem$drug=='PTZ',])*100),2), '%)', sep='')
restab$p[35]<-chisq.test(table(CF, drug))$p.value

restab$variable[36]<- 'LOS (mean[SD])'
restab$AS[36]<-
paste(round(mean(dem$LENGTH_OF_STAY_NUM[drug=='AS'], na.rm = T),2),
' (', round(sd(dem$LENGTH_OF_STAY_NUM[drug=='AS'], na.rm = T),2),')'
, sep='')
restab$PTZ[36]<-
paste(round(mean(dem$LENGTH_OF_STAY_NUM[drug=='PTZ'], na.rm = T),2),
' (', round(sd(dem$LENGTH_OF_STAY_NUM[drug=='PTZ'], na.rm = T),2),'
)', sep='')
restab$p[36]<-t.test(dem$LENGTH_OF_STAY_NUM~drug)$p.value

restab$variable[37]<- 'LOS (median [IQR])'
restab$AS[37]<-
paste(median(dem$LENGTH_OF_STAY_NUM[drug=='AS'], na.rm=T), " (", qua
ntile(dem$LENGTH_OF_STAY_NUM[drug=='AS'], probs=0.25, na.rm = T), '-
',

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      quantile(dem$LENGTH_OF_STAY_NUM[drug=='AS'], pr
obs=0.75, na.rm = T), ')', sep='')
restab$PTZ[37]<-
paste(median(dem$LENGTH_OF_STAY_NUM[drug=='PTZ'], na.rm=T), " (", qu
antile(dem$LENGTH_OF_STAY_NUM[drug=='PTZ'], probs=0.25, na.rm = T), '
-',
      quantile(dem$LENGTH_OF_STAY_NUM[drug=='PTZ']
, probs=0.75, na.rm = T), ')', sep='')
restab$p[37]<-wilcox.test(dem$LENGTH_OF_STAY_NUM~drug)$p.value

# restab$variable[38]<-'icu_admit'
# restab$AS[38]<-
paste(nrow(dem[dem$icu_admit==1 & dem$drug=='AS',]), ' (',
#
      round((nrow(dem[dem$icu_admit==1 & dem$drug==
'AS',])/nrow(dem[dem$drug=='AS',])*100),2), '%)', sep='')
# restab$PTZ[38]<-
paste(nrow(dem[dem$icu_admit==1 & dem$drug=='PTZ',]), ' (',
#
      round((nrow(dem[dem$icu_admit==1 & dem$dru
g=='PTZ',])/nrow(dem[dem$drug=='PTZ',])*100),2), '%)', sep='')
# restab$p[38]<-chisq.test(table(icu_admit, drug))$p.value

# restab$variable[39]<-'Drug'
# restab$variable[40]<-'PTZ'
# restab$AS[40]<-
paste(nrow(dem[dem$drug=='P' & dem$drug=='AS',]), ' (',
#
      round((nrow(dem[dem$drug=='P' & dem$drug=='AS
',])/nrow(dem[dem$drug=='AS',])*100),2), '%)', sep='')
# restab$PTZ[40]<-
paste(nrow(dem[dem$drug=='P' & dem$drug=='PTZ',]), ' (',
#
      round((nrow(dem[dem$drug=='P' & dem$drug==
'PTZ',])/nrow(dem[dem$drug=='PTZ',])*100),2), '%)', sep='')
# restab$variable[41]<-'CFP'
# restab$AS[41]<-
paste(nrow(dem[dem$drug=='C' & dem$drug=='AS',]), ' (',
#
      round((nrow(dem[dem$drug=='C' & dem$drug=='AS
',])/nrow(dem[dem$drug=='AS',])*100),2), '%)', sep='')
# restab$PTZ[41]<-
paste(nrow(dem[dem$drug=='C' & dem$drug=='PTZ',]), ' (',
#
      round((nrow(dem[dem$drug=='C' & dem$drug==
'PTZ',])/nrow(dem[dem$drug=='PTZ',])*100),2), '%)', sep='')
# restab$variable[42]<-'MEM'
# restab$AS[42]<-
paste(nrow(dem[dem$drug=='M' & dem$drug=='AS',]), ' (',
#
      round((nrow(dem[dem$drug=='M' & dem$drug=='AS
',])/nrow(dem[dem$drug=='AS',])*100),2), '%)', sep='')
# restab$PTZ[42]<-
paste(nrow(dem[dem$drug=='M' & dem$drug=='PTZ',]), ' (',
#
      round((nrow(dem[dem$drug=='M' & dem$drug==
'PTZ',])/nrow(dem[dem$drug=='PTZ',])*100),2), '%)', sep='')

```

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#
# restab$p[39]<-chisq.test(table(drug, drug))$p.value

restab$variable[45]<- 'AKI'
restab$variable[46]<- 'Any'
restab$AS[46]<-
paste(nrow(dem[dem$aki==1 & dem$drug=='AS',]), ' (',
      round((nrow(dem[dem$aki==1 & dem$drug=='AS',])/
nrow(dem[dem$drug=='AS',])*100),2), '%)', sep='')
restab$PTZ[46]<-
paste(nrow(dem[dem$aki==1 & dem$drug=='PTZ',]), ' (',
      round((nrow(dem[dem$aki==1 & dem$drug=='PTZ',
,])/nrow(dem[dem$drug=='PTZ',])*100),2), '%)', sep='')
restab$p[46]<-chisq.test(table(aki, drug))$p.value

restab$variable[47]<- 'Risk'
restab$AS[47]<-
paste(nrow(dem[dem$RIFLE=='risk' & dem$drug=='AS',]), ' (',
      round((nrow(dem[dem$RIFLE=='risk' & dem$drug=='
AS',])/nrow(dem[dem$drug=='AS',])*100),2), '%)', sep='')
restab$PTZ[47]<-
paste(nrow(dem[dem$RIFLE=='risk' & dem$drug=='PTZ',]), ' (',
      round((nrow(dem[dem$RIFLE=='risk' & dem$drug
=='PTZ',])/nrow(dem[dem$drug=='PTZ',])*100),2), '%)', sep='')
restab$variable[48]<- 'injury'
restab$AS[48]<-
paste(nrow(dem[dem$RIFLE=='injury' & dem$drug=='AS',]), ' (',
      round((nrow(dem[dem$RIFLE=='injury' & dem$drug=
'AS',])/nrow(dem[dem$drug=='AS',])*100),2), '%)', sep='')
restab$PTZ[48]<-
paste(nrow(dem[dem$RIFLE=='injury' & dem$drug=='PTZ',]), ' (',
      round((nrow(dem[dem$RIFLE=='injury' & dem$dr
ug=='PTZ',])/nrow(dem[dem$drug=='PTZ',])*100),2), '%)', sep='')

restab$variable[49]<- 'failure'
restab$AS[49]<-
paste(nrow(dem[dem$RIFLE=='failure' & dem$drug=='AS',]), ' (',
      round((nrow(dem[dem$RIFLE=='failure' & dem$drug
=='AS',])/nrow(dem[dem$drug=='AS',])*100),2), '%)', sep='')
restab$PTZ[49]<-
paste(nrow(dem[dem$RIFLE=='failure' & dem$drug=='PTZ',]), ' (',
      round((nrow(dem[dem$RIFLE=='failure' & dem$d
rug=='PTZ',])/nrow(dem[dem$drug=='PTZ',])*100),2), '%)', sep='')

restab<-restab[!is.na(restab$variable),]
restab$p[restab$p <=0.00001]<-0.00001
restab$p<-round(restab$p, 5)
write.csv(restab, 'unmatched_results_table.csv', row.names=F)
detach(dem)

```

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#####
#####

mattab<-
data.frame(variable = rep(NA,100), AS = NA, PTZ = NA, p=NA)
mattab$variable[1] = 'N'
mattab$AS[1] = paste(nrow(matdem[matdem$drug=='AS',]), " (", (round(
nrow(matdem[matdem$drug=='AS',])/nrow(matdem),3)*100), '%)', sep='')

mattab$PTZ[1] = paste(nrow(matdem[matdem$drug=='PTZ',]), " (", (roun
d(nrow(matdem[matdem$drug=='PTZ',])/nrow(matdem),3)*100), '%)', sep='
')

attach(matdem)

mattab$variable[2]<- 'Age (mean[SD])'
mattab$AS[2]<-
paste(round(mean(AGE[drug=='AS'], na.rm = T),2), ' (', round(sd(AGE[
drug=='AS'], na.rm = T),2), ')', sep='')
mattab$PTZ[2]<-
paste(round(mean(AGE[drug=='PTZ'], na.rm = T),2), ' (', round(sd(AGE
[drug=='PTZ'], na.rm = T),2), ')', sep='')
mattab$p[2]<-t.test(AGE~drug)$p.value

mattab$variable[3]<- 'Age (median [IQR])'
mattab$AS[3]<-
paste(median(AGE[drug=='AS'], na.rm=T), " (", quantile(AGE[drug=='AS
'], probs=0.25, na.rm = T), '- ',
      quantile(AGE[drug=='AS'], probs=0.75, na.rm = T)
, ')', sep='')
mattab$PTZ[3]<-
paste(median(AGE[drug=='PTZ'], na.rm=T), " (", quantile(AGE[drug=='P
TZ'], probs=0.25, na.rm = T), '- ',
      quantile(AGE[drug=='PTZ'], probs=0.75, na.rm
= T), ')', sep='')
mattab$p[3]<-wilcox.test(AGE~drug)$p.value

mattab$variable[4]<- 'Gender'
mattab$variable[5]<- 'Male'
mattab$AS[5]<-
paste(nrow(matdem[matdem$GENDR_CD_DES=='MALE' & matdem$drug=='AS',])
, ' (',
      round((nrow(matdem[matdem$GENDR_CD_DES=='MALE' &
matdem$drug=='AS',])/nrow(matdem[matdem$drug=='AS',])*100),2), '%)'
, sep='')
mattab$PTZ[5]<-
paste(nrow(matdem[matdem$GENDR_CD_DES=='MALE' & matdem$drug=='PTZ',]
), ' (',
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round((nrow(matdem[matdem$GENDR_CD_DES=='MALE
' & matdem$drug=='PTZ',])/nrow(matdem[matdem$drug=='PTZ',])*100),2),
'%)', sep='')
mattab$variable[6]<-'Female'
mattab$AS[6]<-
paste(nrow(matdem[matdem$GENDR_CD_DES=='FEMALE' & matdem$drug=='AS',
]), ' (',
round((nrow(matdem[matdem$GENDR_CD_DES=='FEMALE'
& matdem$drug=='AS',])/nrow(matdem[matdem$drug=='AS',])*100),2), '%)
)', sep='')
mattab$PTZ[6]<-
paste(nrow(matdem[matdem$GENDR_CD_DES=='FEMALE' & matdem$drug=='PTZ'
,]), ' (',
round((nrow(matdem[matdem$GENDR_CD_DES=='FEMA
LE' & matdem$drug=='PTZ',])/nrow(matdem[matdem$drug=='PTZ',])*100),2
), '%)', sep='')
mattab$p[4]<-chisq.test(table(GENDR_CD_DES, drug))$p.value

mattab$variable[7]<-'caucasian'
mattab$AS[7]<-
paste(nrow(matdem[matdem$caucasian==1 & matdem$drug=='AS',]), ' (',
round((nrow(matdem[matdem$caucasian==1 & matdem$
drug=='AS',])/nrow(matdem[matdem$drug=='AS',])*100),2), '%)', sep='')
mattab$PTZ[7]<-
paste(nrow(matdem[matdem$caucasian==1 & matdem$drug=='PTZ',]), ' (',
round((nrow(matdem[matdem$caucasian==1 & matd
em$drug=='PTZ',])/nrow(matdem[matdem$drug=='PTZ',])*100),2), '%)', s
ep='')
mattab$p[7]<-chisq.test(table(caucasian, drug))$p.value

mattab$variable[8]<-'WT (mean[SD])'
mattab$AS[8]<-
paste(round(mean(INIT_WT[drug=='AS'], na.rm = T),2), ' (', round(sd(
INIT_WT[drug=='AS'], na.rm = T),2), ')', sep='')
mattab$PTZ[8]<-
paste(round(mean(INIT_WT[drug=='PTZ'], na.rm = T),2), ' (', round(sd
(INIT_WT[drug=='PTZ'], na.rm = T),2), ')', sep='')
mattab$p[8]<-t.test(INIT_WT~drug)$p.value

mattab$variable[9]<-'WT (median [IQR])'
mattab$AS[9]<-
paste(median(INIT_WT[drug=='AS'], na.rm=T), " (", quantile(INIT_WT[d
rug=='AS'], probs=0.25, na.rm = T), '-',
quantile(INIT_WT[drug=='AS'], probs=0.75, na.rm
= T), ')', sep='')

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mattab$PTZ[9]<-
paste(median(INIT_WT[drug=='PTZ'], na.rm=T), " (", quantile(INIT_WT[
drug=='PTZ'], probs=0.25, na.rm = T), '- ',
      quantile(INIT_WT[drug=='PTZ'], probs=0.75, na
.rm = T), ')', sep='')
mattab$p[9]<-wilcox.test(INIT_WT~drug)$p.value

mattab$variable[10]<- 'BMI (mean[SD])'
mattab$AS[10]<-
paste(round(mean(BMI[drug=='AS'], na.rm = T),2), ' (', round(sd(BMI[
drug=='AS'], na.rm = T),2), ')', sep='')
mattab$PTZ[10]<-
paste(round(mean(BMI[drug=='PTZ'], na.rm = T),2), ' (', round(sd(BMI
[drug=='PTZ'], na.rm = T),2), ')', sep='')
mattab$p[10]<-t.test(BMI~drug)$p.value

mattab$variable[11]<- 'BMI (median [IQR])'
mattab$AS[11]<-
paste(round(median(BMI[drug=='AS'], na.rm=T),2), " (", round(quantil
e(BMI[drug=='AS'], probs=0.25, na.rm = T),2), '- ',
      round(quantile(BMI[drug=='AS'], probs=0.75, na.
rm = T),2), ')', sep='')
mattab$PTZ[11]<-
paste(round(median(BMI[drug=='PTZ'], na.rm=T),2), " (", round(quantil
e(BMI[drug=='PTZ'], probs=0.25, na.rm = T),2), '- ',
      round(quantile(BMI[drug=='PTZ'], probs=0.75,
na.rm = T),2), ')', sep='')
mattab$p[11]<-wilcox.test(BMI~drug)$p.value

mattab$variable[12]<- 'COMORBIDITY_SCORE (mean[SD])'
mattab$AS[12]<-
paste(round(mean(matdem$COMORBIDITY_SCORE[drug=='AS'], na.rm = T),2)
, ' (', round(sd(matdem$COMORBIDITY_SCORE[drug=='AS'], na.rm = T),2)
, ')', sep='')
mattab$PTZ[12]<-
paste(round(mean(matdem$COMORBIDITY_SCORE[drug=='PTZ'], na.rm = T),2)
), ' (', round(sd(matdem$COMORBIDITY_SCORE[drug=='PTZ'], na.rm = T),
2), ')', sep='')
mattab$p[12]<-t.test(matdem$COMORBIDITY_SCORE~drug)$p.value

mattab$variable[13]<- 'COMORBIDITY_SCORE (median [IQR])'
mattab$AS[13]<-
paste(median(matdem$COMORBIDITY_SCORE[drug=='AS'], na.rm=T), " (", q
uantile(matdem$COMORBIDITY_SCORE[drug=='AS'], probs=0.25, na.rm = T)
, '- ',
      quantile(matdem$COMORBIDITY_SCORE[drug=='AS'],
probs=0.75, na.rm = T), ')', sep='')
mattab$PTZ[13]<-
paste(median(matdem$COMORBIDITY_SCORE[drug=='PTZ'], na.rm=T), " (",

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quantile(matdem$COMORBIDITY_SCORE[drug=='PTZ'], probs=0.25, na.rm =
T), '- ',
                quantile(matdem$COMORBIDITY_SCORE[drug=='PTZ
'], probs=0.75, na.rm = T), ')', sep='')
mattab$p[13]<-wilcox.test(matdem$COMORBIDITY_SCORE~drug)$p.value

mattab$variable[14]<-'baseline crcl (mean[SD])'
mattab$AS[14]<-
paste(round(mean(matdem$baseline_crcl[drug=='AS'], na.rm = T),2), '
(', round(sd(matdem$baseline_crcl[drug=='AS'], na.rm = T),2), ')', se
p='')
mattab$PTZ[14]<-
paste(round(mean(matdem$baseline_crcl[drug=='PTZ'], na.rm = T),2), '
(', round(sd(matdem$baseline_crcl[drug=='PTZ'], na.rm = T),2), ')',
sep='')
mattab$p[14]<-t.test(matdem$baseline_crcl~drug)$p.value

mattab$variable[15]<-'baseline crcl (median [IQR])'
mattab$AS[15]<-
paste(round(median(matdem$baseline_crcl[drug=='AS'], na.rm=T),2), "
(",
                round(quantile(matdem$baseline_crcl[drug=='AS']
, probs=0.25, na.rm = T),2), '- ',
                round(quantile(matdem$baseline_crcl[drug=='AS']
, probs=0.75, na.rm = T),2), ')', sep='')
mattab$PTZ[15]<-
paste(round(median(matdem$baseline_crcl[drug=='PTZ'], na.rm=T),2), "
(",
                round(quantile(matdem$baseline_crcl[drug=='P
TZ'], probs=0.25, na.rm = T),2), '- ',
                round(quantile(matdem$baseline_crcl[drug=='P
TZ'], probs=0.75, na.rm = T),2), ')', sep='')
mattab$p[15]<-wilcox.test(matdem$baseline_crcl~drug)$p.value

mattab$variable[16]<-'baseline crcl drug'
mattab$variable[17]<-'30-59 mL/min'
mattab$AS[17]<-
paste(nrow(matdem[matdem$baseline_crcl_cat == 1 & matdem$drug=='AS',
]), ' (',
                round((nrow(matdem[matdem$baseline_crcl_cat ==
1 & matdem$drug=='AS', ])/nrow(matdem[matdem$drug=='AS', ])*100),2), '
%)', sep='')
mattab$PTZ[17]<-
paste(nrow(matdem[matdem$baseline_crcl_cat == 1 & matdem$drug=='PTZ'
, ]), ' (',
                round((nrow(matdem[matdem$baseline_crcl_cat
== 1 & matdem$drug=='PTZ', ])/nrow(matdem[matdem$drug=='PTZ', ])*100),
2), '%)', sep='')
mattab$variable[18]<-'60-89 mL/min'

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mattab$AS[18]<-
paste(nrow(matdem[matdem$baseline_crcl_cat == 2 & matdem$drug=='AS',
]), ' (',
      round((nrow(matdem[matdem$baseline_crcl_cat ==
2 & matdem$drug=='AS',])/nrow(matdem[matdem$drug=='AS',])*100),2), '
%)', sep='')
mattab$PTZ[18]<-
paste(nrow(matdem[matdem$baseline_crcl_cat == 2 & matdem$drug=='PTZ'
,]), ' (',
      round((nrow(matdem[matdem$baseline_crcl_cat
== 2 & matdem$drug=='PTZ',])/nrow(matdem[matdem$drug=='PTZ',])*100),
2), '%)', sep='')
mattab$variable[19]<- '>=90 mL/min'
mattab$AS[19]<-
paste(nrow(matdem[matdem$baseline_crcl_cat == 3 & matdem$drug=='AS',
]), ' (',
      round((nrow(matdem[matdem$baseline_crcl_cat ==
3 & matdem$drug=='AS',])/nrow(matdem[matdem$drug=='AS',])*100),2), '
%)', sep='')
mattab$PTZ[19]<-
paste(nrow(matdem[matdem$baseline_crcl_cat == 3 & matdem$drug=='PTZ'
,]), ' (',
      round((nrow(matdem[matdem$baseline_crcl_cat
== 3 & matdem$drug=='PTZ',])/nrow(matdem[matdem$drug=='PTZ',])*100),
2), '%)', sep='')
mattab$p[16]<-chisq.test(table(baseline_crcl_cat, drug))$p.value

mattab$variable[20]<- 'Concomitant nephrotoxins'
mattab$variable[21]<- 'Aminoglycosides'
mattab$AS[21]<-
paste(nrow(matdem[matdem$aminoglycoside_exp == 1 & matdem$drug=='AS'
,]), ' (',
      round((nrow(matdem[matdem$aminoglycoside_exp ==
1 & matdem$drug=='AS',])/nrow(matdem[matdem$drug=='AS',])*100),2),
      '%)', sep='')
mattab$PTZ[21]<-
paste(nrow(matdem[matdem$aminoglycoside_exp == 1 & matdem$drug=='PTZ'
,]), ' (',
      round((nrow(matdem[matdem$aminoglycoside_exp
== 1 & matdem$drug=='PTZ',])/nrow(matdem[matdem$drug=='PTZ',])*100)
,2),
      '%)', sep='')
mattab$p[21]<-chisq.test(table(aminoglycoside_exp, drug))$p.value

mattab$variable[22]<- 'amphb'
mattab$AS[22]<-
paste(nrow(matdem[matdem$amphb_exp == 1 & matdem$drug=='AS',]), ' ( '
,

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round((nrow(matdem[matdem$amphb_exp == 1 & matdem$drug=='AS', ])/nrow(matdem[matdem$drug=='AS', ])*100),2),
      '%)', sep='')
mattab$PTZ[22]<-
paste(nrow(matdem[matdem$amphb_exp == 1 & matdem$drug=='PTZ', ]), ' (',
      round((nrow(matdem[matdem$amphb_exp == 1 & matdem$drug=='PTZ', ])/nrow(matdem[matdem$drug=='PTZ', ])*100),2),
      '%)', sep='')
mattab$p[22]<-chisq.test(table(amphb_exp, drug))$p.value

mattab$variable[23]<- 'acei'
mattab$AS[23]<-
paste(nrow(matdem[matdem$acei_exp == 1 & matdem$drug=='AS', ]), ' (',
      round((nrow(matdem[matdem$acei_exp == 1 & matdem$drug=='AS', ])/nrow(matdem[matdem$drug=='AS', ])*100),2),
      '%)', sep='')
mattab$PTZ[23]<-
paste(nrow(matdem[matdem$acei_exp == 1 & matdem$drug=='PTZ', ]), ' (',
      round((nrow(matdem[matdem$acei_exp == 1 & matdem$drug=='PTZ', ])/nrow(matdem[matdem$drug=='PTZ', ])*100),2),
      '%)', sep='')
mattab$p[23]<-chisq.test(table(acei_exp, drug))$p.value

mattab$variable[24]<- 'arb'
mattab$AS[24]<-
paste(nrow(matdem[matdem$arb_exp == 1 & matdem$drug=='AS', ]), ' (',
      round((nrow(matdem[matdem$arb_exp == 1 & matdem$drug=='AS', ])/nrow(matdem[matdem$drug=='AS', ])*100),2),
      '%)', sep='')
mattab$PTZ[24]<-
paste(nrow(matdem[matdem$arb_exp == 1 & matdem$drug=='PTZ', ]), ' (',
      round((nrow(matdem[matdem$arb_exp == 1 & matdem$drug=='PTZ', ])/nrow(matdem[matdem$drug=='PTZ', ])*100),2),
      '%)', sep='')
mattab$p[24]<-chisq.test(table(arb_exp, drug))$p.value

mattab$variable[25]<- 'cont'
mattab$AS[25]<-
paste(nrow(matdem[matdem$cont_exp == 1 & matdem$drug=='AS', ]), ' (',
      round((nrow(matdem[matdem$cont_exp == 1 & matdem$drug=='AS', ])/nrow(matdem[matdem$drug=='AS', ])*100),2),
      '%)', sep='')

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mattab$PTZ[25]<-
paste(nrow(matdem[matdem$cont_exp == 1 & matdem$drug=='PTZ',]), ' ( '
,
      round((nrow(matdem[matdem$cont_exp == 1 & ma
tdem$drug=='PTZ',])/nrow(matdem[matdem$drug=='PTZ',])*100),2),
      '%)', sep='')
mattab$p[25]<-chisq.test(table(cont_exp, drug))$p.value

mattab$variable[26]<- 'loop'
mattab$AS[26]<-
paste(nrow(matdem[matdem$loop_exp == 1 & matdem$drug=='AS',]), ' ( '
,
      round((nrow(matdem[matdem$loop_exp == 1 & matde
m$drug=='AS',])/nrow(matdem[matdem$drug=='AS',])*100),2),
      '%)', sep='')
mattab$PTZ[26]<-
paste(nrow(matdem[matdem$loop_exp == 1 & matdem$drug=='PTZ',]), ' ( '
,
      round((nrow(matdem[matdem$loop_exp == 1 & ma
tdem$drug=='PTZ',])/nrow(matdem[matdem$drug=='PTZ',])*100),2),
      '%)', sep='')
mattab$p[26]<-chisq.test(table(loop_exp, drug))$p.value

mattab$variable[27]<- 'nsaids'
mattab$AS[27]<-
paste(nrow(matdem[matdem$nsaids_exp == 1 & matdem$drug=='AS',]), ' ( '
,
      round((nrow(matdem[matdem$nsaids_exp == 1 & mat
dem$drug=='AS',])/nrow(matdem[matdem$drug=='AS',])*100),2),
      '%)', sep='')
mattab$PTZ[27]<-
paste(nrow(matdem[matdem$nsaids_exp == 1 & matdem$drug=='PTZ',]), ' ( '
( '
,
      round((nrow(matdem[matdem$nsaids_exp == 1 &
matdem$drug=='PTZ',])/nrow(matdem[matdem$drug=='PTZ',])*100),2),
      '%)', sep='')
mattab$p[27]<-chisq.test(table(nsaids_exp, drug))$p.value

mattab$variable[28]<- 'calc'
mattab$AS[28]<-
paste(nrow(matdem[matdem$calc_exp == 1 & matdem$drug=='AS',]), ' ( '
,
      round((nrow(matdem[matdem$calc_exp == 1 & matde
m$drug=='AS',])/nrow(matdem[matdem$drug=='AS',])*100),2),
      '%)', sep='')
mattab$PTZ[28]<-
paste(nrow(matdem[matdem$calc_exp == 1 & matdem$drug=='PTZ',]), ' ( '
,

```

```

round((nrow(matdem[matdem$calc_exp == 1 & matdem$drug=='PTZ',])/nrow(matdem[matdem$drug=='PTZ',])*100),2),
      '%)', sep='')
mattab$p[28]<-chisq.test(table(calc_exp, drug))$p.value

# mattab$variable[29]<-'vanc'
# mattab$AS[29]<-
paste(nrow(matdem[matdem$vanc_exp == 1 & matdem$drug=='AS',]), ' (',
      round((nrow(matdem[matdem$vanc_exp == 1 & matdem$drug=='AS',])/nrow(matdem[matdem$drug=='AS',])*100),2),
      '%)', sep='')
# mattab$PTZ[29]<-
paste(nrow(matdem[matdem$vanc_exp == 1 & matdem$drug=='PTZ',]), ' (',
      round((nrow(matdem[matdem$vanc_exp == 1 & matdem$drug=='PTZ',])/nrow(matdem[matdem$drug=='PTZ',])*100),2),
      '%)', sep='')
# mattab$p[29]<-chisq.test(table(vanc_exp, drug))$p.value

mattab$variable[30]<-'vaso'
mattab$AS[30]<-
paste(nrow(matdem[matdem$vaso_exp == 1 & matdem$drug=='AS',]), ' (',
      round((nrow(matdem[matdem$vaso_exp == 1 & matdem$drug=='AS',])/nrow(matdem[matdem$drug=='AS',])*100),2),
      '%)', sep='')
mattab$PTZ[30]<-
paste(nrow(matdem[matdem$vaso_exp == 1 & matdem$drug=='PTZ',]), ' (',
      round((nrow(matdem[matdem$vaso_exp == 1 & matdem$drug=='PTZ',])/nrow(matdem[matdem$drug=='PTZ',])*100),2),
      '%)', sep='')
mattab$p[30]<-chisq.test(table(vaso_exp, drug))$p.value

mattab$variable[31]<-'Comorbidities'
mattab$variable[32]<-'DM'
mattab$AS[32]<-
paste(nrow(matdem[matdem$dm==1 & matdem$drug=='AS',]), ' (',
      round((nrow(matdem[matdem$dm==1 & matdem$drug=='AS',])/nrow(matdem[matdem$drug=='AS',])*100),2), '%)', sep='')
mattab$PTZ[32]<-
paste(nrow(matdem[matdem$dm==1 & matdem$drug=='PTZ',]), ' (',
      round((nrow(matdem[matdem$dm==1 & matdem$drug=='PTZ',])/nrow(matdem[matdem$drug=='PTZ',])*100),2), '%)', sep='')
mattab$p[32]<-chisq.test(table(matdem$dm, drug))$p.value

mattab$variable[33]<-'HF'

```

```

mattab$AS[33]<-
paste(nrow(matdem[matdem$hf==1 & matdem$drug=='AS',]), ' (',
      round((nrow(matdem[matdem$hf==1 & matdem$drug==
'AS',])/nrow(matdem[matdem$drug=='AS',])*100),2), '%)', sep='')
mattab$PTZ[33]<-
paste(nrow(matdem[matdem$hf==1 & matdem$drug=='PTZ',]), ' (',
      round((nrow(matdem[matdem$hf==1 & matdem$dru
g=='PTZ',])/nrow(matdem[matdem$drug=='PTZ',])*100),2), '%)', sep='')

mattab$p[33]<-chisq.test(table(matdem$hf, drug))$p.value

mattab$variable[34]<- 'HTN'
mattab$AS[34]<-
paste(nrow(matdem[matdem$HTN==1 & matdem$drug=='AS',]), ' (',
      round((nrow(matdem[matdem$HTN==1 & matdem$drug=
'AS',])/nrow(matdem[matdem$drug=='AS',])*100),2), '%)', sep='')
mattab$PTZ[34]<-
paste(nrow(matdem[matdem$HTN==1 & matdem$drug=='PTZ',]), ' (',
      round((nrow(matdem[matdem$HTN==1 & matdem$dru
g=='PTZ',])/nrow(matdem[matdem$drug=='PTZ',])*100),2), '%)', sep='
')
mattab$p[34]<-chisq.test(table(HTN, drug))$p.value

mattab$variable[35]<- 'CF'
mattab$AS[35]<-
paste(nrow(matdem[matdem$CF==1 & matdem$drug=='AS',]), ' (',
      round((nrow(matdem[matdem$CF==1 & matdem$drug==
'AS',])/nrow(matdem[matdem$drug=='AS',])*100),2), '%)', sep='')
mattab$PTZ[35]<-
paste(nrow(matdem[matdem$CF==1 & matdem$drug=='PTZ',]), ' (',
      round((nrow(matdem[matdem$CF==1 & matdem$dru
g=='PTZ',])/nrow(matdem[matdem$drug=='PTZ',])*100),2), '%)', sep='')

mattab$p[35]<-chisq.test(table(CF, drug))$p.value

mattab$variable[36]<- 'LOS (mean[SD])'
mattab$AS[36]<-
paste(round(mean(matdem$LENGTH_OF_STAY_NUM[drug=='AS'], na.rm = T),2
), ' (', round(sd(matdem$LENGTH_OF_STAY_NUM[drug=='AS'], na.rm = T),
2), ')', sep='')
mattab$PTZ[36]<-
paste(round(mean(matdem$LENGTH_OF_STAY_NUM[drug=='PTZ'], na.rm = T),
2), ' (', round(sd(matdem$LENGTH_OF_STAY_NUM[drug=='PTZ'], na.rm = T
),2), ')', sep='')
mattab$p[36]<-t.test(matdem$LENGTH_OF_STAY_NUM~drug)$p.value

mattab$variable[37]<- 'LOS (median [IQR])'
mattab$AS[37]<-
paste(median(matdem$LENGTH_OF_STAY_NUM[drug=='AS'], na.rm=T), " (",

```

```

quantile(matdem$LENGTH_OF_STAY_NUM[drug=='AS'], probs=0.25, na.rm =
T), '- ',
      quantile(matdem$LENGTH_OF_STAY_NUM[drug=='AS'],
probs=0.75, na.rm = T), ')', sep='')
mattab$PTZ[37]<-
paste(median(matdem$LENGTH_OF_STAY_NUM[drug=='PTZ'], na.rm=T), " (",
quantile(matdem$LENGTH_OF_STAY_NUM[drug=='PTZ'], probs=0.25, na.rm
= T), '- ',
      quantile(matdem$LENGTH_OF_STAY_NUM[drug=='PT
Z'], probs=0.75, na.rm = T), ')', sep='')
mattab$p[37]<-wilcox.test(matdem$LENGTH_OF_STAY_NUM~drug)$p.value

# mattab$variable[38]<-'icu_admit'
# mattab$AS[38]<-
paste(nrow(matdem[matdem$icu_admit==1 & matdem$drug=='AS',]), ' (',
#
      round((nrow(matdem[matdem$icu_admit==1 & matd
em$drug=='AS',])/nrow(matdem[matdem$drug=='AS',])*100),2), '%)', sep
='')
# mattab$PTZ[38]<-
paste(nrow(matdem[matdem$icu_admit==1 & matdem$drug=='PTZ',]), ' (',
#
      round((nrow(matdem[matdem$icu_admit==1 & m
atdem$drug=='PTZ',])/nrow(matdem[matdem$drug=='PTZ',])*100),2), '%)'
, sep='')
# mattab$p[38]<-chisq.test(table(icu_admit, drug))$p.value

# mattab$variable[39]<-'Drug'
# mattab$variable[40]<-'PTZ'
# mattab$AS[40]<-
paste(nrow(matdem[matdem$drug=='P' & matdem$drug=='AS',]), ' (',
#
      round((nrow(matdem[matdem$drug=='P' & matdem$
drug=='AS',])/nrow(matdem[matdem$drug=='AS',])*100),2), '%)', sep=''
)
# mattab$PTZ[40]<-
paste(nrow(matdem[matdem$drug=='P' & matdem$drug=='PTZ',]), ' (',
#
      round((nrow(matdem[matdem$drug=='P' & matd
em$drug=='PTZ',])/nrow(matdem[matdem$drug=='PTZ',])*100),2), '%)', s
ep='')
# mattab$variable[41]<-'CFP'
# mattab$AS[41]<-
paste(nrow(matdem[matdem$drug=='C' & matdem$drug=='AS',]), ' (',
#
      round((nrow(matdem[matdem$drug=='C' & matdem$
drug=='AS',])/nrow(matdem[matdem$drug=='AS',])*100),2), '%)', sep=''
)
# mattab$PTZ[41]<-
paste(nrow(matdem[matdem$drug=='C' & matdem$drug=='PTZ',]), ' (',

```

```

#                                     round((nrow(matdem[matdem$drug=='C' & matdem$drug=='PTZ', ])/nrow(matdem[matdem$drug=='PTZ', ])*100),2), '%)', sep='')
# mattab$variable[42]<- 'MEM'
# mattab$AS[42]<-
paste(nrow(matdem[matdem$drug=='M' & matdem$drug=='AS', ]), ' (',
#                                     round((nrow(matdem[matdem$drug=='M' & matdem$drug=='AS', ])/nrow(matdem[matdem$drug=='AS', ])*100),2), '%)', sep='')
)
# mattab$PTZ[42]<-
paste(nrow(matdem[matdem$drug=='M' & matdem$drug=='PTZ', ]), ' (',
#                                     round((nrow(matdem[matdem$drug=='M' & matdem$drug=='PTZ', ])/nrow(matdem[matdem$drug=='PTZ', ])*100),2), '%)', sep='')
)
#
# mattab$p[39]<-chisq.test(table(drug, drug))$p.value

mattab$variable[45]<- 'AKI'
mattab$variable[46]<- 'Any'
mattab$AS[46]<-
paste(nrow(matdem[matdem$aki==1 & matdem$drug=='AS', ]), ' (',
#                                     round((nrow(matdem[matdem$aki==1 & matdem$drug=='AS', ])/nrow(matdem[matdem$drug=='AS', ])*100),2), '%)', sep='')
)
mattab$PTZ[46]<-
paste(nrow(matdem[matdem$aki==1 & matdem$drug=='PTZ', ]), ' (',
#                                     round((nrow(matdem[matdem$aki==1 & matdem$drug=='PTZ', ])/nrow(matdem[matdem$drug=='PTZ', ])*100),2), '%)', sep='')
)
mattab$p[46]<-chisq.test(table(aki, drug))$p.value

mattab$variable[47]<- 'Risk'
mattab$AS[47]<-
paste(nrow(matdem[matdem$RIFLE=='risk' & matdem$drug=='AS', ]), ' (',
#                                     round((nrow(matdem[matdem$RIFLE=='risk' & matdem$drug=='AS', ])/nrow(matdem[matdem$drug=='AS', ])*100),2), '%)', sep='')
)
mattab$PTZ[47]<-
paste(nrow(matdem[matdem$RIFLE=='risk' & matdem$drug=='PTZ', ]), ' (',
#                                     round((nrow(matdem[matdem$RIFLE=='risk' & matdem$drug=='PTZ', ])/nrow(matdem[matdem$drug=='PTZ', ])*100),2), '%)', sep='')
)
mattab$variable[48]<- 'injury'
mattab$AS[48]<-
paste(nrow(matdem[matdem$RIFLE=='injury' & matdem$drug=='AS', ]), ' (',
#                                     round((nrow(matdem[matdem$RIFLE=='injury' & matdem$drug=='AS', ])/nrow(matdem[matdem$drug=='AS', ])*100),2), '%)', sep='')
)

```

```

round((nrow(matdem[matdem$RIFLE=='injury' & matdem$drug=='AS',])/nrow(matdem[matdem$drug=='AS',])*100),2), '%', sep='')
mattab$PTZ[48]<-
paste(nrow(matdem[matdem$RIFLE=='injury' & matdem$drug=='PTZ',]), '
(',
round((nrow(matdem[matdem$RIFLE=='injury' & matdem$drug=='PTZ',])/nrow(matdem[matdem$drug=='PTZ',])*100),2), '%', sep='')

mattab$variable[49]<- 'failure'
mattab$AS[49]<-
paste(nrow(matdem[matdem$RIFLE=='failure' & matdem$drug=='AS',]), '
(',
round((nrow(matdem[matdem$RIFLE=='failure' & matdem$drug=='AS',])/nrow(matdem[matdem$drug=='AS',])*100),2), '%', sep='')
mattab$PTZ[49]<-
paste(nrow(matdem[matdem$RIFLE=='failure' & matdem$drug=='PTZ',]), '
(',
round((nrow(matdem[matdem$RIFLE=='failure' & matdem$drug=='PTZ',])/nrow(matdem[matdem$drug=='PTZ',])*100),2), '%', sep='')

mattab<-mattab[!is.na(mattab$variable),]
mattab$p[mattab$p <=0.00001]<-0.00001
mattab$p<-round(mattab$p, 5)
1. write.csv(mattab, 'matched_results_table.csv', row.names=F)

```


Appendix D: Chapter 5 code

R code used to clean data

```
library(data.table)
dat<-
fread('d:/Dissertation Data/crcl_data.csv', colClasses='character')

head(dat)
dat$V1=NULL
dat$date = as.Date(dat$date)
dat$crcl = as.numeric(dat$crcl)

eids = unique(dat$ENCNTR_ID)

#dat_b = dat
#dat=dat[1:100]
#dat = dat_b

for(i in eids){
  x = dat[dat$ENCNTR_ID == i,]
  dat$baseline_crcl[dat$ENCNTR_ID==i] = x$crcl[1]
}
base_crcls = dat[,c('ENCNTR_ID', 'baseline_crcl')]
base_crcls = unique(base_crcls)

dat$pct_change = (dat$crcl/dat$baseline_crcl)-1
head(dat)
table(dat$pct_change < -0.25)

demo = fread('D:/Dissertation Data/RUTTER_846_ENCOUNTERS.csv', colClasses='character')
head(demo)
demo = demo[demo$ENCNTR_ID %in% eids,]
demo$ad_date = sapply(strsplit(demo$ADMT_DT, ' '), '[' ,1)
demo$ad_date = as.Date(demo$ad_date)
demo$dc_date = sapply(strsplit(demo$DISCHRG_DT, ' '), '[' , 1)
demo$dc_date = as.Date(demo$dc_date)
demo$los = as.numeric(demo$dc_date - demo$ad_date)
summary(demo$los)
demo = demo[demo$los >=2,]

dup_eids = demo[duplicated(demo$ENCNTR_ID)]
demo_dups = demo[demo$ENCNTR_ID %in% dup_eids$ENCNTR_ID,]

demo = demo[!demo$ENCNTR_ID %in% demo_dups$ENCNTR_ID,]
for(i in unique(demo_dups$ENCNTR_ID)){
  x = demo_dups[demo_dups$ENCNTR_ID==i,]
```

```

x = x[x$ad_date == min(x$ad_date)]
demo = rbind(demo, x)
}
rm(demo_dups, dup_eids, x, tmp_list)

demo = merge(demo, base_crcls, by = 'ENCNTR_ID', all=T)
demo$F_NAME<-NULL
demo$L_NAME= NULL
head(demo)

demo$AGE<-as.numeric(demo$AGE)

dat$AKI[dat$pct_change <=-0.25]=1
dat$AKI[is.na(dat$AKI)]=0
aki_eids = dat$ENCNTR_ID[dat$AKI==1]
aki_eids = unique(aki_eids)

dat$RIFLE[dat$pct_change <=-0.25 & dat$pct_change >-0.5]<-'risk'
dat$RIFLE[dat$pct_change <=-0.5 & dat$pct_change >-0.75]<-'injury'
dat$RIFLE[dat$pct_change <=-0.75]<-'failure'
dat$RIFLE[is.na(dat$RIFLE)]<-'none'
table(dat$RIFLE, dat$AKI)

demo$AKI[demo$ENCNTR_ID %in% aki_eids]=1
demo$AKI[is.na(demo$AKI)]=0
table(demo$AKI )

demo = demo[demo$GENDR_CD_DES !='UNKNOWN',]
table(demo$GENDR_CD_DES)

for(i in aki_eids){
  x = dat[dat$ENCNTR_ID == i,]
  x = x[x$AKI==1,]
  aki_date = min(x$date)
  demo$aki_date[demo$ENCNTR_ID == i]=aki_date
}

demo$aki_date = as.Date(demo$aki_date, origin = '1970-01-01')
head(demo)

cbtx = fread('R codes/first_combo_tx_date.csv', colClasses='character')
cbtx = cbtx[cbtx$Vancomycin==1,]
cbtx = cbtx[cbtx$ENCNTR_ID %in% demo$ENCNTR_ID]
demo = demo[demo$ENCNTR_ID %in% cbtx$ENCNTR_ID]
str(cbtx)

combo_dates = cbtx[,c('ENCNTR_ID', 'date')]
names(combo_dates)[2]<-'combo_tx_date'

```

```

demo = merge(demo, combo_dates, by='ENCNTR_ID', all=T)
head(demo)
demo$combo_tx_date<-as.Date(demo$combo_tx_date)
table(demo$aki_date>= demo$combo_tx_date+2)
str(demo)

demo$index_date = demo$combo_tx_date+2
eid_dates = demo[,c('ENCNTR_ID','index_date')]
write.csv(eid_dates, 'R codes/eid_index_dates.csv',row.names=F)
#####
#dat_b<-dat
#dat<-dat_b
dat<-merge(dat, eid_dates, by='ENCNTR_ID', all=T)
dat$tx_aki[dat$AKI == 1 & dat$date >= dat$index_date]=1
dat$tx_aki[is.na(dat$tx_aki)]<-0

aki_eids=unique(dat$ENCNTR_ID[dat$tx_aki==1])
table(demo$AKI)
demo$AKI=0
demo$AKI[demo$ENCNTR_ID %in% aki_eids]=1
table(demo$AKI)
head(demo)

demo<-demo[demo$index_date>=demo$ad_date,]
study_days = data.frame(ENCNTR_ID =NA, date=NA)
for(i in 1:nrow(demo)){
  date_range = seq(demo$ad_date[i], demo$index_date[i], by=1)
  study_days = rbind(study_days, data.frame(ENCNTR_ID= demo$ENCNTR_ID[i], date=date_range))
}
study_days = study_days[!is.na(study_days$date),]
study_days$date = as.Date(study_days$date, origin= '1970-01-01')
View(tail(study_days, 1000))

new_study_days = data.frame()
for(i in unique(study_days$ENCNTR_ID)){
  x = study_days[study_days$ENCNTR_ID==i,]
  x$day = seq(nrow(x)-1, 0, by = -1)
  new_study_days = rbind(new_study_days, x)
}
rm(study_days)
summary(new_study_days$day)

max_days = data.frame()
for(i in unique(new_study_days$ENCNTR_ID)){
  x = new_study_days[new_study_days$ENCNTR_ID == i,]
  x = max(x$day)
  max_days = rbind(max_days,x)
}

```

```

hist(max_days$X2, breaks = 100) # shows small % of max_days > 60 mos
t <30
summary(max_days)
rm(max_days)

new_study_days = new_study_days[new_study_days$day<=30,]
summary(new_study_days)
table(demo$ENCNTR_ID %in% new_study_days$ENCNTR_ID)
write.csv(demo, 'pt_demo.csv', row.names=F)
write.csv(new_study_days, 'study_days.csv', row.names=F)

rm(list= setdiff(ls(), c('demo', 'new_study_days')))
#####
labs = fread('labs 21618.csv', colClasses='character')
labs = labs[labs$ENCNTR_ID %in% new_study_days$ENCNTR_ID,]
labs$date = sapply(strsplit(labs$ENTERED, ' '), '[' ,1)
labs = merge(new_study_days, labs, by=c('ENCNTR_ID', 'date'), all.x=
T)
head(labs)
labs$V1=NULL

labs$val_num=as.numeric(labs$VAL_NUM)
labs_num = labs[!is.na(labs$val_num),]
labs_cat = labs[is.na(labs$val_num),]
nrow(labs) == nrow(labs_num) + nrow(labs_cat) #all obs kept
rm(labs)
head(labs_num)
lab_limits = as.data.frame(labs_num[,c('CODE', 'REFERENCE_LOWER_LIMIT
', 'REFERENCE_UPPER_LIMIT')])
lab_limits = unique(lab_limits)
#lab_limits$ITEM_NAME<-
gsub(pattern = 'zzz', lab_limits$ITEM_NAME, replacement = '')
lab_limits$REFERENCE_LOWER_LIMIT = as.numeric(lab_limits$REFERENCE_L
OWER_LIMIT)
lab_limits$REFERENCE_UPPER_LIMIT = as.numeric(lab_limits$REFERENCE_U
PPER_LIMIT)
lab_dups <- lab_limits$CODE[duplicated(lab_limits$CODE)]
lab_limits$f1g[lab_limits$CODE %in% lab_dups & (is.na(lab_limits$REF
ERENCE_LOWER_LIMIT) |
is.na(lab_limits$R
EFERENCE_UPPER_LIMIT))] = 1
lab_limits$f1g[is.na(lab_limits$f1g)]=0
lab_limits=lab_limits[lab_limits$f1g==0,]
lab_dups <- lab_limits$CODE[duplicated(lab_limits$CODE)]
lab_dups = lab_limits[lab_limits$CODE %in% lab_dups,]
lab_dups = lab_dups[order(lab_dups$CODE),]

for(i in 1:nrow(lab_limits)){

```

```

x = labs_num[labs_num$CODE == lab_limits$CODE[i],]
x = x[x$REFERENCE_LOWER_LIMIT == lab_limits$REFERENCE_LOWER_LIMIT[
i],]
x = x[x$REFERENCE_UPPER_LIMIT == lab_limits$REFERENCE_UPPER_LIMIT[
i],]
lab_limits$ct[i] = nrow(x)
}
summary(lab_limits$ct)
new_lab_lim=data.frame()
for(i in unique(lab_limits$CODE)){
x = lab_limits[lab_limits$CODE == i,]
x = x[x$ct==max(x$ct),]
new_lab_lim = rbind(new_lab_lim, x)
}
names(new_lab_lim) = c('CODE','LL','UL','flg','ct')
new_lab_lim$flg=NULL
new_lab_lim$ct = NULL
labs_num$REFERENCE_LOWER_LIMIT=NULL
labs_num$REFERENCE_UPPER_LIMIT=NULL
labs_num = merge(labs_num, new_lab_lim, by='CODE', all=T)

# View(table(labs_num$ITEM_NAME[is.na(labs_num$REFERENCE_LOWER_LIMIT
)]))

names(labs_num)
labs_num$val[labs_num$val_num < labs_num$LL]<-'low'
labs_num$val[labs_num$val_num > labs_num$UL]<-'high'
labs_num$val[labs_num$val_num >= labs_num$LL &
labs_num$val_num <= labs_num$UL] = 'norm'
labs_num$val[is.na(labs_num$val)]='perf'
table(labs_num$val)

keep_vars = c('ENCNTR_ID','day','CODE','val')
labs_num = labs_num[,keep_vars]
labs_num$var = paste('L_',labs_num$CODE,'_D',labs_num$day,sep='')
head(labs_num$var)
class(labs_num)
labs_num<-as.data.table(labs_num)
labs_num$val_n = as.numeric(factor(labs_num$val, levels = c('perf','
low','norm','high'), ordered = T))
labs_num_cast = dcast(labs_num, ENCNTR_ID~var, value.var = 'val_n',
fun.aggregate = max)
#View(head(labs_num_cast[,100:200])) # lots if -
inf need to replace with NA or 0?
labs_num_cast<-as.data.frame(labs_num_cast)
for( i in 1:ncol(labs_num_cast)) set(labs_num_cast, which(is.infinite(labs_num_cast[[i]])), i , 0)

demo = merge(demo, labs_num_cast, by='ENCNTR_ID', all.y=T)

```

```

#View(head(demo[1:100]))
rm(labs_num_cast, labs_num, lab_limits, lab_dups, new_lab_lim)

#####
# Now that numeric labs are added we can look at the categorical lab
# s
# IE did they perform lab without numeric returns
#
####
head(labs_cat)
labs_cat$var = paste('L_',labs_cat$CODE, '_D',labs_cat$day,sep='')
labs_cat = as.data.table(labs_cat)
labs_cat$n = 1
summary(labs_cat$day)
labs_cat_cast = dcast(labs_cat, ENCNTR_ID ~ var, value.var = 'n')
head(labs_cat_cast[,1:100],5)

keep_vars = names(labs_cat_cast)[!(names(labs_cat_cast) %in% names(d
emo))]
keep_vars = c('ENCNTR_ID', keep_vars)
labs_cat_cast = labs_cat_cast[,keep_vars]
demo=merge(demo, labs_cat_cast, by='ENCNTR_ID',all=T)
#####
rm(list=setdiff(ls(),c('demo','new_study_days')))
meds = fread('RUTTER_MEDS.txt', colClasses='character', sep='\t')
meds = meds[meds$ENCNTR_ID %in% demo$ENCNTR_ID,]
head(meds)
keep_vars = c('ENCNTR_ID', 'DRUG_KEY', 'PERFORMED_FROM_DTM')
meds = as.data.frame(meds)
meds = meds[,keep_vars]
head(meds)
meds$date = sapply(strsplit(meds$PERFORMED_FROM_DTM, ' '), '[', 1)
meds$PERFORMED_FROM_DTM<-NULL
meds$date = as.Date(meds$date)
meds = merge(new_study_days, meds, by=c('ENCNTR_ID', 'date'), all.x
=T)
meds = as.data.table(meds)
meds$n = 1
meds = meds[meds$DRUG_KEY!='NULL',]

meds$var = paste(meds$DRUG_KEY, '_D',meds$day, sep='')
meds.cast = dcast(meds, ENCNTR_ID ~ var, value.var = 'n' )

demo = merge(demo, meds.cast, by='ENCNTR_ID', all=T)
rm(meds, meds.cast)
names(demo)[47000:47100]
#####
vit = fread('//file2/crutter/dissertation/vitals 2118.csv', colClass
es='character')

```

```

head(vit)
vit = vit[vit$ENCNTR_ID %in% demo$ENCNTR_ID,]
vit = as.data.frame(vit)
vit$ADMIT_DTM = NULL
vit$date = sapply(strsplit(vit$RECRD_DT_TM, ' '), '[',1)
vit$RECRD_DT_TM=NULL
head(vit)
keep_vars = c('ENCNTR_ID', 'date', 'FIO2', 'RESP_RT', 'SPO2', 'DIR_SYSTOL
IC', 'DIR_DIASTOLIC', 'BLOODGLUC', 'HEART_RT',
              'TEMP')
vit = vit[,keep_vars]
vit = as.data.table(vit)
vit = melt(vit, id.vars = c('ENCNTR_ID', 'date'))
vit = vit[!is.na(vit$value),]

vit$date=as.Date(vit$date)

vit = merge(vit, new_study_days, by=c('ENCNTR_ID', 'date'), all.y=T)

vit=vit[!is.na(vit$day),]
vit$value = as.numeric(vit$value)
by(vit$value, vit$variable, summary) ### NEED TO GET RID OF STUPID O
UTLIERS
# next steps - get rid out outliers
vits_cuts = fread('C:/users/crutter/desktop/vital_ranges_table.csv',
  stringsAsFactors = F)
vits_cuts$LC = NA
vits_cuts$UC = NA
for(i in vits_cuts$Vital){
  #print(summary(vit.cast$value[vit.cast$variable==i]))
  vits_cuts$LC[vits_cuts$Vital ==i] = (mean(vit$value[vit$variable==
i], na.rm=T) -
                                     4*sd(vit$value[vit$variable
==i], na.rm=T))
  vits_cuts$UC[vits_cuts$Vital ==i] = (mean(vit$value[vit$variable==
i], na.rm=T) +
                                     4*sd(vit$value[vit$variable
==i], na.rm=T))
}
vits_cuts$LC[vits_cuts$LC<0]=0
fio2 = vit[vit$variable== 'FIO2',]
vit = vit[vit$variable != 'FIO2',]
vit = merge(vit, vits_cuts, by.x = 'variable',by.y='Vital', all=T)
vit = vit[vit$value <= vit$UC & vit$value >=vit$LC,]

vit.cast = dcast(vit, ENCNTR_ID+day~variable, value.var = 'value', f
un.aggregate = median)
vit.cast = melt(vit.cast, id.vars = c('ENCNTR_ID', 'day'))
vit.cast = vit.cast[!is.na(vit.cast$value),]

```

```

by(vit.cast$value, vit.cast$variable, summary)
# Then - set up upper and lower limits
vit.cast = merge(vit.cast, vits_cuts, by.x = 'variable', by.y='Vital'
, all=T)
vit.cast$LC = NULL
vit.cast$UC = NULL
vit.cast$val_cat[vit.cast$value < vit.cast$LL]=1
vit.cast$val_cat[vit.cast$value >= vit.cast$LL & vit.cast$value <=vi
t.cast$UL]=2
vit.cast$val_cat[vit.cast$value > vit.cast$UL]=3
table(vit.cast$val_cat) # verify that all values have been evaluated

vit.cast$val = paste(vit.cast$variable, '_D_', vit.cast$day, sep='')

# then cast
vit.cast = dcast(vit.cast, ENCNTN_ID ~ val, value.var='val_cat')
for( i in 1:ncol(vit.cast)) set(vit.cast, which(is.na(vit.cast[[i]]))
), i , 0)

demo = merge(demo, vit.cast, by='ENCNTN_ID')
rm(vit, vit.cast, vits_cuts, keep_vars, i, fio2)
##### save cause vitals take too long
save.image("C:/Users/crutter/Desktop/merge lab codes3618.RData")
#####
icu = fread('c:/users/crutter/desktop/RUTTER_846_ICU_R_AND_B.csv', c
olClasses='character')
head(icu)

icu = icu[icu$ENCNTN_ID %in% demo$ENCNTN_ID,]
icu$date = as.Date(icu$SERVC_DT)
icu$SERVC_DT = NULL
icu = merge(new_study_days, icu, by=c('ENCNTN_ID', 'date'))
icu$var = paste('ICU_D_', icu$day, sep='')
table(icu$var)
eids = data.frame(ENCNTN_ID = demo$ENCNTN_ID)
icu = dcast(icu, ENCNTN_ID~var, value.var='QTY')
icu = merge(eids, icu, by='ENCNTN_ID', all=T)
icu[is.na(icu)]<-0

#demo_b = demo
#demo =demo_b
demo = merge(demo, icu , by='ENCNTN_ID')
rm(icu, eids, demo_b)
####
dx = fread('c:/users/crutter/desktop/RUTTER_846_DIAGNOSIS2.txt', col
Classes='character')
dx = dx[dx$ENCNTN_ID %in% demo$ENCNTN_ID,]
head(dx)
dx = dx[dx$DIAGNOSIS !='584.9',]

```



```

dx$code = paste('ICD9_', dx$DIAGNOSIS, sep='')
head(dx)
dx$n=1
dx = dcast(dx, ENCNTR_ID~code, value.var = 'n')

#demo_b = demo
#demo =demo_b

demo = merge(demo, dx, by='ENCNTR_ID')
demo_b = demo
demo$ad_date =NULL
demo$dc_date = NULL
demo$los = NULL
demo$aki_date = NULL
demo$RETIRED_FLG = NULL
demo$MRN = NULL
demo$ADMT_DT = NULL
demo$DISCHRG_DT=NULL
demo$DISCHRG_DISP_CD_DES=NULL
demo$BIRTH_DT=NULL
demo$combo_tx_date=NULL
demo$index_date=NULL
demo$ETHNCTY_CD_DES[demo$ETHNCTY_CD_DES=='NULL']='UNKNOWN'
demo$RACE_CD_DES[demo$RACE_CD_DES=='NULL']='UNKNOWN'
save.image("C:/Users/crutter/Desktop/merge lab codes3618.RData")
write.csv(demo, 'c:/users/crutter/desktop/final_dis_data.csv', row.names=F)

#### subset for 7 day look back
names(demo)[1:10]
keep_names = names(demo)[1:7]
d7_names = names(demo)[grepl('D0$', names(demo))|
grepl('D1$', names(demo))|
grepl('D2$', names(demo))|
grepl('D3$', names(demo))|
grepl('D4$', names(demo))|
grepl('D5$', names(demo))|
grepl('D6$', names(demo))|
grepl('D7$', names(demo))|
grepl('D_0$', names(demo))|
grepl('D_1$', names(demo))|
grepl('D_2$', names(demo))|
grepl('D_3$', names(demo))|
grepl('D_4$', names(demo))|
grepl('D_5$', names(demo))|
grepl('D_6$', names(demo))|
grepl('D_7$', names(demo))|
grepl('^ICD', names(demo))]

```

```
demo_sub = demo[,c(keep_names, d7_names)]
write.csv(demo_sub, 'C:/users/crutter/desktop/final_subset_data.csv'
, row.names=F)
```

Python code for machine learning model development

```
#Begin imports
import sklearn.naive_bayes as sknb
import pandas as pd
import numpy as np
import sklearn.metrics as met
from sklearn.utils import shuffle
from sklearn.metrics import confusion_matrix
from sklearn import preprocessing as pe
from sklearn.svm import SVC
from sklearn.externals import joblib
from sklearn.ensemble import RandomForestClassifier
from sklearn import linear_model
import keras
from keras import backend as K
from sklearn.model_selection import train_test_split
from sklearn.utils import shuffle
from keras.utils.np_utils import to_categorical
from keras.callbacks import EarlyStopping
from keras.models import load_model
#End Imports

def fbeta(tp, tn, fp, fn, beta =1):
    b=beta**2
    f = ((1+b)*tp)/((1+b)*tp + b*fn + fp)

model_metrics = []

dat = pd.read_csv('c:/users/wru224/desktop/test_sub_dat.csv')
dat.drop('ENCNTR_ID', axis=1, inplace=True)
dat.info()
dat = shuffle(dat, random_state=123)
dat = pd.get_dummies(dat, drop_first=True )
dat.dropna(inplace=True)
dat.info()
y=dat['AKI'].values
dat.drop('AKI', axis=1, inplace=True)
var_names=dat.columns

dat = dat.values
X_train, X_test, y_train, y_test = train_test_split(dat, y, test_size = 0.05 )
early_stop_monitor = EarlyStopping(patience=2)
```

```

#####
# March 6, 2018 - first model
# Two 100 node Relu layers with a 2 node softmax layer
#####
model = keras.models.Sequential()
model.add(keras.layers.Dense(100, activation='relu', input_shape=(data.shape[1],)))
model.add(keras.layers.Dense(100, activation='relu'))
model.add(keras.layers.Dense(2, activation='softmax'))
model.summary()
model.compile(optimizer='adam', loss='sparse_categorical_crossentropy', metrics=['accuracy'] )

model.fit(X_train, y_train, validation_split=0.1, callbacks=[early_stopping_monitor], verbose=False)
#model = load_model('c:/users/wru224/desktop/dissertation/models/NN_model_1_3618.h5')
y_pred = model.predict(X_test)
y_pred_pos = y_pred[:,1]
y_pred_pos = np.round(y_pred_pos)
tn, fp, fn, tp = confusion_matrix(y_test, y_pred_pos).ravel()
acc=(tp+tn)/(tp+tn+fp+fn)
prec= tp/(tp+fp)
recall = tp/(tp+fn)
f1= met.f1_score(y_pred=y_pred_pos, y_true=y_test)
MCC = met.matthews_corrcoef(y_test, y_pred_pos)
metrics = ["NN_Model_1_3618", tp, tn, fp, fn, acc, prec, recall, f1, MCC]
model_metrics.append(metrics)
print('====NN_Model_1_3618 Neural Network====\n',
      'tp=', tp, '\n',
      'tn=', tn, '\n',
      'fp=', fp, '\n',
      'fn=', fn, '\n',
      'acc=', acc, '\n',
      'prec=', prec, '\n',
      'recall=', recall, '\n',
      'f1=', f1, '\n',
      'MCC=', MCC, '\n')
model.save('c:/users/wru224/desktop/dissertation/models/NN_model_1_3618.h5')
#####
#####
model = keras.models.Sequential()
model.add(keras.layers.Dense(100, activation='relu', input_shape=(data.shape[1],)))
model.add(keras.layers.Dense(100, activation='relu'))

```

```

model.add(keras.layers.Dense(100, activation='relu'))
model.add(keras.layers.Dense(2, activation='softmax'))
model.summary()
model.compile(optimizer='adam', loss='sparse_categorical_crossentropy', metrics=['accuracy'] )

model.fit(X_train, y_train, validation_split=0.1, callbacks=[early_stop_monitor])
#model = load_model('c:/users/wru224/desktop/dissertation/models/NN_model_2_3618.h5')
y_pred = model.predict(X_test)
y_pred_pos = y_pred[:,1]
y_pred_pos = np.round(y_pred_pos)
tn, fp, fn, tp = confusion_matrix(y_test, y_pred_pos).ravel()
acc=(tp+tn)/(tp+tn+fp+fn)
prec= tp/(tp+fp)
recall = tp/(tp+fn)
f1 =met.f1_score(y_pred=y_pred_pos, y_true=y_test)
MCC = met.matthews_corrcoef(y_test, y_pred_pos)
metrics = ["NN_Model_2_3618", tp, tn, fp, fn, acc, prec, recall, f1, MCC]
model_metrics.append(metrics)
print('=====NN_Model_2_3618 Neural Network=====\\n',
      'tp=', tp, '\\n',
      'tn=', tn, '\\n',
      'fp=', fp, '\\n',
      'fn=', fn, '\\n',
      'acc=', acc, '\\n',
      'prec=', prec, '\\n',
      'recall=', recall, '\\n',
      'f1=', f1, '\\n',
      'MCC=', MCC, '\\n')
model.save('c:/users/wru224/desktop/dissertation/models/NN_model_2_3618.h5')
#####
#####
model = keras.models.Sequential()
model.add(keras.layers.Dense(500, activation='relu', input_shape=(data.shape[1],)))
model.add(keras.layers.Dense(100, activation='relu'))
model.add(keras.layers.Dense(2, activation='softmax'))
model.summary()
model.compile(optimizer='adam', loss='sparse_categorical_crossentropy', metrics=['accuracy'] )
model.fit(X_train, y_train, validation_split=0.1, callbacks=[early_stop_monitor], verbose=False)
y_pred = model.predict(X_test)
y_pred_pos = y_pred[:,1]
y_pred_pos = np.round(y_pred_pos)

```

```

tn, fp, fn, tp = confusion_matrix(y_test, y_pred_pos).ravel()
acc=(tp+tn)/(tp+tn+fp+fn)
prec= tp/(tp+fp)
recall = tp/(tp+fn)
f1 =met.f1_score(y_pred=y_pred_pos, y_true=y_test)
MCC = met.matthews_corrcoef(y_test, y_pred_pos)
metrics = ["NN_Model_3_3618", tp, tn, fp, fn, acc, prec, recall, f1,
MCC]
model_metrics.append(metrics)
print('====NN_Model_3_3618 Neural Network====\n',
'tp=', tp, '\n',
'tn=', tn, '\n',
'fp=', fp, '\n',
'fn=', fn, '\n',
'acc=', acc, '\n',
'prec=', prec, '\n',
'recall=', recall, '\n',
'f1=', f1, '\n',
'MCC=', MCC, '\n')
model.save('c:/users/wru224/desktop/dissertation/models/NN_model_3_3
618.h5')

#####
model = keras.models.Sequential()
model.add(keras.layers.Dense(100, activation='relu', input_shape=(da
t.shape[1],)))
model.add(keras.layers.Dropout(0.2))
model.add(keras.layers.Dense(100, activation='relu'))
model.add(keras.layers.Dropout(0.2))
model.add(keras.layers.Dense(2, activation='softmax'))
model.summary()
model.compile(optimizer='adam', loss='sparse_categorical_crossentropy',
metrics=['accuracy'] )

model.fit(X_train, y_train, validation_split=0.1, callbacks=[early_s
top_monitor], verbose=False)
y_pred = model.predict(X_test)
y_pred_pos = y_pred[:,1]
y_pred_pos = np.round(y_pred_pos)
tn, fp, fn, tp = confusion_matrix(y_test, y_pred_pos).ravel()
acc=(tp+tn)/(tp+tn+fp+fn)
prec= tp/(tp+fp)
recall = tp/(tp+fn)
f1= met.f1_score(y_pred=y_pred_pos, y_true=y_test)
MCC = met.matthews_corrcoef(y_test, y_pred_pos)
metrics = ["NN_Model_4_3618", tp, tn, fp, fn, acc, prec, recall, f1,
MCC]
model_metrics.append(metrics)
print('====NN_Model_4_3618 Neural Network====\n',

```

```

        'tp=', tp, '\n',
        'tn=', tn, '\n',
        'fp=', fp, '\n',
        'fn=', fn, '\n',
        'acc=', acc, '\n',
        'prec=', prec, '\n',
        'recall=', recall, '\n',
        'f1=', f1, '\n',
        'MCC=', MCC, '\n')
model.save('c:/users/wru224/desktop/dissertation/models/NN_model_4_3
618.h5')

#####
##
clf = sknb.BernoulliNB()
clf.fit(X_train, y_train)
y_pred = clf.predict(X_test)
tn, fp, fn, tp = confusion_matrix(y_test, y_pred).ravel()
acc=(tp+tn)/(tp+tn+fp+fn)
prec= tp/(tp+fp)
recall = tp/(tp+fn)
f1= met.f1_score(y_test, y_pred)
MCC = met.matthews_corrcoef(y_test, y_pred)
metrics = ["NB", tp, tn, fp, fn, acc, prec, recall, f1, MCC]
model_metrics.append(metrics)
print('=====Naive Bayes=====\n',
        'tp=', tp, '\n',
        'tn=', tn, '\n',
        'fp=', fp, '\n',
        'fn=', fn, '\n',
        'acc=', acc, '\n',
        'prec=', prec, '\n',
        'recall=', recall, '\n',
        'f1=', f1, '\n',
        'MCC=', MCC, '\n')

#####
#####
rfclf = RandomForestClassifier()
rfclf.fit(X_train, y_train)
rf_pred = rfclf.predict(X_test)
tn, fp, fn, tp = confusion_matrix(y_test, rf_pred).ravel()
acc=(tp+tn)/(tp+tn+fp+fn)
prec= tp/(tp+fp)
recall = tp/(tp+fn)
f1= met.f1_score(y_pred= rf_pred, y_true= y_test)
MCC = met.matthews_corrcoef(y_test, rf_pred)
metrics = ["RF", tp, tn, fp, fn, acc, prec, recall, f1, MCC]
print('=====Random Forest=====\n',

```

```

        'tp=', tp, '\n',
        'tn=', tn, '\n',
        'fp=', fp, '\n',
        'fn=', fn, '\n',
        'acc=', acc, '\n',
        'prec=', prec, '\n',
        'recall=', recall, '\n',
        'f1=', f1, '\n',
        'MCC=', MCC, '\n')

#####
#####
fit= linear_model.LogisticRegression(C=1.0, penalty='l2',tol=1e-6)
fit.fit(X=X_train, y=y_train )
test_pred = fit.predict(X_test)
tn, fp, fn, tp = confusion_matrix(y_test, test_pred).ravel()
acc=(tp+tn)/(tp+tn+fp+fn)
prec= tp/(tp+fp)
recall = tp/(tp+fn)
f1= met.f1_score(test_pred, y_test)
MCC = met.matthews_corrcoef(y_test, test_pred)
metrics = ["L2", tp, tn, fp, fn, acc, prec, recall, f1, MCC]
print('====L2 regression====\n',
        'tp=', tp, '\n',
        'tn=', tn, '\n',
        'fp=', fp, '\n',
        'fn=', fn, '\n',
        'acc=', acc, '\n',
        'prec=', prec, '\n',
        'recall=', recall, '\n',
        'f1=', f1, '\n',
        'MCC=', MCC, '\n')
model_metrics.append(metrics)

model_metrics_df = pd.DataFrame(model_metrics)
model_metrics_df.columns = ['model', 'TP', 'TN', 'FP', 'FN', 'ACC', 'PREC',
, 'RECALL', 'F1_score', 'MCC']
model_metrics_df

```

Appendix E: Summary of machine learning methods

Rationale

Attempting to predict the occurrence of an acute kidney injury in patients receiving broad-spectrum antimicrobials is a question of classification. We treat the AKI and non-AKI patients as distinct binary classes. Several methods exist to predict a class based on known information. Due to the nature of this problem, supervised learning can be utilized. Supervised learning relies on the presence of known outcomes and predictors. In the case of predicting AKI, patient-specific laboratory data can be leveraged to identify AKI using published AKI criteria. In our case we used the RIFLE criteria(19) to identify significant changes in creatinine clearance. The risk, injury, and failure categories present and evaluated in RIFLE were collapsed into a binary indicator variable for AKI vs. no AKI.

Prior to completing the machine-learning tasks, the clinical data must be preprocessed to streamline computation. In the case of categorical variables with multiple categories (ie. Non-binary variables), variables were converted using one-hot encoding (Figure E.1). Briefly, the presence of a feature is encoded as a 1 while the absence is encoded 0. For the laboratory data example, a patient might have multiple labs obtained on the same day. If the results were discordant, for example, one draw was high and the other normal, both the high and normal flag for that lab on that day would be 1 while the low flag would be 0. While this strategy limits inference into the sequence of events, it allows us to capture multiple data points for specific features that might otherwise be missed.

Naïve Bayes classifier

The Naïve Bayes classifier (NB) is a probabilistic classifier based on Bayes theorem in which the condition probability of an event (A) given that a second event (B) has occurred is

dependent on the conditional probability of B given A, the probability of A, and the probability of B.

$$P(A|B) = \frac{P(B|A)P(A)}{P(B)}$$

In the presented research, the conditional probability of AKI occurring is dependent on the interactions between the conditional probability of each feature in the dataset occurring if an AKI occurred and the individual probabilities of the feature values occurring. The NB classifier is “naïve” due to the strong assumption of independent probabilities.

Regularized logistic regression

In this study, L2 regularized logistic regression (L2) was utilized to predict AKI occurrence. This was primarily done to minimize overfitting that may occur with traditional logistic regression (LR) methods. The primary difference between L2 and traditional LR is the addition of a weight penalty to minimize the potential for learning large parameter estimates that may occur with significant overfitting. While this method decreases test-train accuracy, it generally improves generalizability to the validation set. The equation for this penalty is shown below with (w) representing the parameter weights and λ represents the hyperparameter to control regularization strength.

$$L2 = \frac{\lambda}{2} \sum_{j=1}^m w_j^2$$

Random Forest Classifier

The random forest classifier (RF) is an ensemble method that acts as an extension of the decision tree classifier. Decision trees tend to overfit data when tree depth is too great, resulting in learning noise present in data. RF classifiers overcome this limitation by fitting many smaller

trees to the data and selecting a subspace of available features and observations. The final step in the process is averaging the resultant model results.

Neural Network models

The fundamental unit of a neural network (NN) is the neuron, or node, which takes a numerical input vector and computes a linear combination followed by a nonlinear activation function. There are three basic layer types in a NN. First is the input layer, which is the data being provided to the model. Second, hidden layers perform the computation previously described and pass data further down the network stream. Finally, the output layer computes a specific activation function to provide the appropriate output for the model. For example, in a classification task such as the projects described, the softmax activation function can be used to determine the most likely class. The softmax function can return the probability for a class, which is important for use a clinical decision support tool. For hidden layers, one of the most commonly used activation function is the rectified linear unit, or ReLU. This function returns the maximum of zero or the linear combination passed to the node. This assists in model development by avoiding vanishing or exploding gradients.

Evaluating models

Formulae for model metrics utilized are shown below.

$$Accuracy = \frac{TP + TN}{Total\ population}$$

$$Precision\ (PPV) = \frac{TP}{(TP + FP)}$$

$$Recall = \frac{TP}{(TP + FN)}$$

$$F1 = \frac{2}{\frac{1}{Recall} + \frac{1}{Precision}}$$

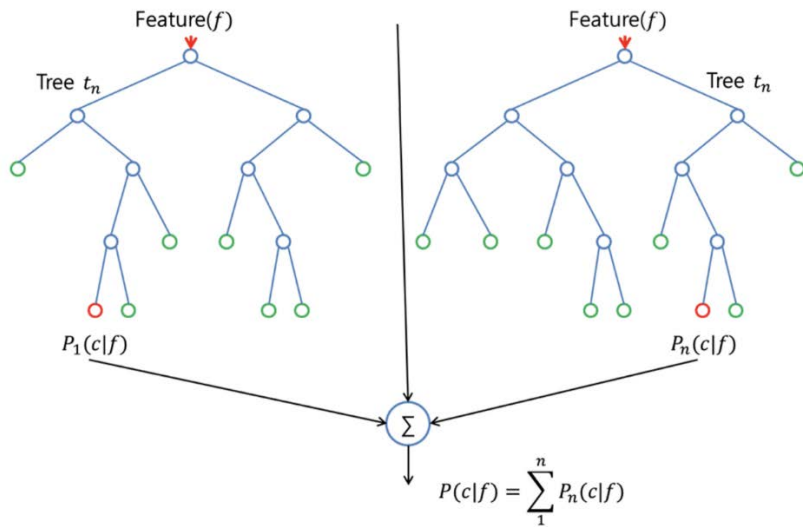
Tables and Figures

Figure E.1 Example of one-hot encoding of categorical variables

| ID | Gender | ID | Male | Female | Not Specified |
|----|---------------|----|------|--------|---------------|
| 1 | Male | 1 | 1 | 0 | 0 |
| 2 | Female | 2 | 0 | 1 | 0 |
| 3 | Not Specified | 3 | 0 | 0 | 1 |
| 4 | Not Specified | 4 | 0 | 0 | 1 |
| 5 | Female | 5 | 0 | 1 | 0 |

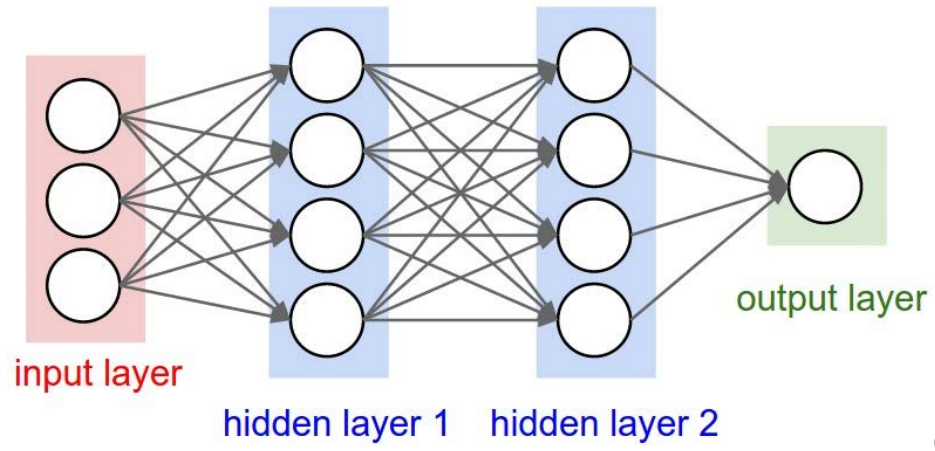
(77)

Figure E.2 Random forest classifier example



(78)

Figure E.3 Neural network architecture (3 layers)



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EDUCATION

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PUBLICATIONS

Manuscripts

Cotner SE, **Rutter WC**, Burgess DR, Wallace KL, Martin CA, Burgess DS. Influence of beta-lactam infusion strategy on acute kidney injury. *Antimicrob Agents Chemother.* 2017 Sep 22;61(10). pii: e00871-17. doi: 10.1128/AAC.00871-17. Print 2017 Oct.

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Abstracts

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Rutter WC, Burgess DS. *Early antimicrobial de-escalation is associated with decreased acute kidney injury in patients receiving empiric combination therapy*. Presented at ID Week 2017; 4-8 Oct 2017; San Diego, CA.

Rutter WC, Burgess DS. *Incidence of acute kidney injury among intensive care unit patients receiving vancomycin in combination with cefepime or piperacillin-tazobactam*. Presented at ID Week 2017; 4-8 Oct 2017; San Diego, CA.

Rutter WC, Burgess DS. *Is there a significant difference in acute kidney injury incidence among patients treated with vancomycin combined with cefepime or meropenem?* Presented at ID Week 2017; 4-8 Oct 2017; San Diego, CA.

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Rutter WC, Burgess DS. *Acute Kidney Injury in Patients Treated with Beta-lactam/Beta-lactamase Inhibitor Combinations*. Presented at ID Week 2016; 26-30 Oct 2016; New Orleans, LA.

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Rutter WC, Lee GC, Burgess DS. *Antimicrobial Susceptibility and Resistomes of Carbapenem Resistant Enterobacteriaceae.* Presented at ASM Microbe 2016; 16-20 June 2016; Boston, MA.

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Rutter WC, Talbert JC, Burgess DS. *Incidence of Acute Kidney Injury in Patients Treated with Vancomycin and Piperacillin/Tazobactam.* Presented at ID Week 2015; 7-11 Oct 2015; San Diego, CA.

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Rutter WC, Burgess DR, Burgess DS. *Increasing Incidence of Multidrug Resistance Among Cystic Fibrosis Respiratory Isolates.* Presented at ID Week 2015; 7-11 Oct 2015; San Diego, CA.

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Rutter WC, Burgess DS. *In vitro characterization of amikacin and polymyxin b therapy in combination with meropenem for carbapenem-resistant Enterobacter cloacae*. Presented at Rho Chi Research Day, University of Kentucky; 17 Apr 2015; Lexington, KY.

Cox JN, **Rutter WC**, Martin CA, Burgess DR, Zephyr D, Burgess DS. *Incidence of Acute Kidney Injury During Therapy with Vancomycin in Combination with Beta-Lactam Antibiotics*. Presented at Rho Chi Research Day, University of Kentucky; 17 Apr 2015; Lexington, KY.

Rutter WC, Wornall SH, Shely CL. *Evaluation of MRSA treatment failures associated with elevated vancomycin minimum inhibitory concentrations in a rural, nonacademic hospital*. Poster presented at: ASHP Midyear clinical meeting 2013; 11 Dec 2013; Orlando, FL.

Rutter WC, Lee G, Burgess D, Winkler K, Burgess DS. *Surveillance of resistance trends of community-acquired versus hospital-acquired urinary tract infections*. Poster presented at: ASHP Midyear clinical meeting 2012; 3 Dec 2012; Las Vegas, NV.

Rutter WC, Burgess D, Winkler K, Lee G, Burgess DS. *Evaluation of epidemiology and susceptibility trends in urinary tract infections over 5 years in a community hospital*. Poster presented at: IDWeek 2012. The 1st joint meeting of the Infectious Disease Society of America, the Society of Healthcare Epidemiology of America, the HIV Medicine Association, and the Pediatric Infectious Disease Society; 17-21 Oct 2012; San Diego, CA.

Rutter WC, Lee G, Burgess D, Winkler K, Burgess DS. *Surveillance of resistance trends of community-acquired versus hospital-acquired urinary tract infections*. Poster presented at: IDWeek 2012. The 1st joint meeting of the Infectious Disease Society of America, the Society of Healthcare Epidemiology of America, the HIV Medicine Association, and the Pediatric Infectious Disease Society; 17-21 Oct 2012; San Diego, CA.

Rutter WC, Burgess D, Winkler K, Dasher T, Burgess DS. *Evaluation of urinary tract infection antimicrobial susceptibility in a community hospital*. Poster presented at: Eighth Annual Louis C. Littlefield Celebrating Pharmacy Research Excellence Day; 17 Apr 2012; Austin, TX.

AWARDS AND GRANTS

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|-------------------|---|
| 10/2017 | IDWeek Trainee Travel Grant |
| 10/2016 | Peter G. Glavinovs, Jr., Ph.D. Travel Award University of Kentucky College of Pharmacy |
| 10/2016 | IDWeek Trainee Travel Grant |
| 11/2015 – 11/2017 | The Medicines Company Infectious Disease Pharmacotherapy Research Award Society of Infectious Disease Pharmacists |
| 10/2015 | IDWeek Trainee Travel Grant |
| 04/2013 | Student Research/Scholarship Award Graduate School of Biomedical Sciences – College of Pharmacy |
| 10/2012 | IDWeek Trainee Travel Grant |
| 05/2008 – 05/2013 | The University of Texas at Austin – University Honors |
| 08/2010 – 08/2012 | Pharmacy Alumni Association Endowed Scholarship |
| 08/2007 – 01/2008 | The National Science & Mathematics Access to Retain Talent (SMART) Grant Recipient |
| 12/2006 | The University of Texas at San Antonio – Dean’s List |