Retrospective, Multicentre Matched Cohort Study
Comparing Safety and Efficacy Outcomes of Intermittent Infusion and Continuous Infusion Vancomycin

by

Nathan Hing-Leong Ma

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Department of Pharmaceutical Sciences
University of Toronto

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Abstract

Patients with good renal function receiving intermittent infusion vancomycin (IIV) may require total daily doses $\geq$4g to achieve trough concentrations of 15-20mg/L, increasing the risk of vancomycin associated nephrotoxicity (VAN). Continuous infusion vancomycin (CIV) may attain concentrations of 15-20mg/L with lower daily doses, potentially reducing the risk of VAN.

A retrospective chart review for eligible patients admitted to hospital between January 1, 2010-December 31, 2016 was completed. Adult patients receiving $\geq$48 hours of vancomycin with $\geq$1 steady state vancomycin concentration were eligible. The primary outcome was to compare the rates of nephrotoxic risk and renal injury, defined by the RIFLE criteria, between CIV and IIV.

Of 2136 patients identified, 146 CIV patients were identified and matched to 146 IIV patients. CIV was found to have a lower odds of developing nephrotoxic risk (odds ratio [OR] 0.42, 95% confidence interval [CI] 0.21-0.98) and renal injury (OR 0.19, 95% CI 0.05-0.59, p=0.004).
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<th>Terminology</th>
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<tr>
<td>95% CI</td>
<td>95% Confidence Interval</td>
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<tr>
<td>ACE</td>
<td>Angiotensin converting enzyme inhibitor</td>
</tr>
<tr>
<td>AKI</td>
<td>Acute kidney injury</td>
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<tr>
<td>AKIN</td>
<td>Acute Kidney Injury Network</td>
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<tr>
<td>APACHE II</td>
<td>Acute Physiology and Chronic Health Evaluation II</td>
</tr>
<tr>
<td>ARB</td>
<td>Angiotensin-receptor blocker</td>
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<tr>
<td>AUC</td>
<td>Area under the curve</td>
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<tr>
<td>AUC&lt;sub&gt;24h&lt;/sub&gt;</td>
<td>24 hour area under the curve</td>
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<tr>
<td>CHF</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>CIV</td>
<td>Continuous infusion vancomycin</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CNST</td>
<td>Coagulase negative <em>Staphylococci</em></td>
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<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>CrCl</td>
<td>Creatinine clearance</td>
</tr>
<tr>
<td>CVVH</td>
<td>Continuous Veno-Venous Hemodialysis</td>
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<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
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<tr>
<td>C&lt;sub&gt;ss&lt;/sub&gt;</td>
<td>Steady state concentration</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>DOA</td>
<td>Date of admission</td>
</tr>
<tr>
<td>DOB</td>
<td>Date of birth</td>
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<tr>
<td>DOD</td>
<td>Date of discharge</td>
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<tr>
<td>EPR</td>
<td>Electronic patient records</td>
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<tr>
<td>GEE</td>
<td>Generalized estimating equation</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>--------------</td>
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<tr>
<td>HFN</td>
<td>Hospital file number</td>
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<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>IDSA</td>
<td>Infectious Diseases Society of America</td>
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<tr>
<td>IIV</td>
<td>Intermittent infusion vancomycin</td>
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<tr>
<td>LD</td>
<td>Loading Dose</td>
</tr>
<tr>
<td>LOS</td>
<td>Length of stay</td>
</tr>
<tr>
<td>MD</td>
<td>Maintenance dose</td>
</tr>
<tr>
<td>MGH</td>
<td>Michael Garron Hospital</td>
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<tr>
<td>MIC</td>
<td>Minimum inhibitory concentration</td>
</tr>
<tr>
<td>MRSA</td>
<td>Methicillin resistant <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>MSSA</td>
<td>Methicillin sensitive <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>NSAID</td>
<td>Nonsteroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>OPAT</td>
<td>Outpatient antibiotic therapy</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>PPI</td>
<td>Proton pump inhibitor</td>
</tr>
<tr>
<td>SHSC</td>
<td>Sunnybrook Health Sciences Centre</td>
</tr>
<tr>
<td>SHSC-BC</td>
<td>Sunnybrook Health Sciences Centre – Bayview Campus</td>
</tr>
<tr>
<td>SHSC-HC</td>
<td>Sunnybrook Health Sciences Centre – Holland Orthopaedic and Arthritic Centre</td>
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<tr>
<td>SHSC-SJR</td>
<td>Sunnybrook Health Sciences Centre – St. John’s Rehab</td>
</tr>
<tr>
<td>SICU</td>
<td>Surgical Intensive Care Unit</td>
</tr>
<tr>
<td>SPIRIT</td>
<td>Stewardship Program Integrating Resources Information Technology</td>
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<tr>
<td>VAN</td>
<td>Vancomycin associated nephrotoxicity</td>
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<tr>
<td>WBC</td>
<td>White blood cell</td>
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Chapter 1

INTRODUCTION
1 Introduction

1.1 A brief history of vancomycin

Penicillin-resistant staphylococci started to become an emerging threat following the discovery and widespread use of antibiotics in the 1940s. [5] In response, Eli Lilly started a program in the 1950s to identify new antibiotics active against these resistant pathogens. [5, 6] A soil sample from Borneo was found to contain *Streptomyces orientalis*, a bacterium that produces a compound with activity against penicillin-resistant staphylococci, *Clostridium* spp., and *Neisseria gonorrhoeae*. [5, 6] Serial passaging the compound with staphylococci did not result in significant resistance. [6] The compound was approved by the United States Food and Drug Administration and given the generic name vancomycin. [5, 6] Initial preparations of vancomycin contained numerous impurities, imparting a brown color and earning it the nickname “Mississippi mud.” [5]

Unfortunately, the excitement surrounding vancomycin quickly waned. Early studies with vancomycin indicated it could cause both nephrotoxicity and ototoxicity. [7-10] Safer semi-synthetic penicillins, like methicillin, that were active against penicillin-resistant staphylococci were developed shortly after. Thus, despite its early promise, vancomycin quickly fell out of favor and was considered second line therapy. However, a rise in the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in the 1980s has led to resurgence in the use of vancomycin. [11]

Vancomycin has been available for almost 70 years and continues to be among the most scrutinized drugs, with countless studies attempting to characterize its pharmacokinetic and pharmacodynamic properties. The dosing recommendations and monitoring parameters have changed numerous times, indicating a lack of agreement on how to optimally dose and monitor the antibiotic. [12, 13]

1.2 Current Infectious Diseases Society of America guideline recommendations for dosing and monitoring vancomycin

The current Infectious Diseases Society of America (IDSA) guidelines [14] recommend dosing vancomycin 15-20mg/kg every 8-12 hours. They support targeting a ratio of the 24 hour area...
under the curve (AUC$_{24h}$) of the total vancomycin concentration-time profile to the minimum inhibitory concentration (MIC) (AUC$_{24h}$:MIC) $\geq$400mg*h/L for complicated infections (e.g. endocarditis, osteomyelitis, pneumonia, etc.) (Level of Evidence and Grade of Recommendation IIIB). However, because AUC$_{24h}$:MIC is difficult to calculate for intermittent infusion vancomycin (IV), they recommend targeting a steady state trough of 15-20mg/L as a surrogate. For non-complicated infections, the guidelines recommend maintaining vancomycin troughs above $>10$mg/L with the rationale of preventing the development of resistance (Level of Evidence and Grade of Recommendation IIIB). [14]

Performing therapeutic drug monitoring is only recommended for patients whose target trough range is 15-20mg/L to minimize the risk of nephrotoxicity. Peak serum vancomycin concentrations are not recommended. Situations where monitoring is also recommended include the following: patients with tenuous renal function, patients receiving concomitant nephrotoxins, or for patients receiving prolonged courses of vancomycin $>3$-5 days. There is little data to support the safety of maintaining trough concentrations of 15-20mg/L for prolonged courses, but patients should have the trough measured once per week. Patients may require more frequent monitoring of serum trough concentrations if they are hemodynamically unstable, but the exact frequency is left up to the clinician’s judgment. [14]

The use of continuous infusion vancomycin (CIV) is currently not recommended. The IDSA guidelines cite the lack of a clearly defined benefit for clinical outcomes and conflicting results comparing the rates of nephrotoxicity as the primary reasons for continuing to use intermittent infusion vancomycin (Level of Evidence and Grade of Recommendation IIA). [14]

### 1.3 Vancomycin pharmacokinetics and pharmacodynamics

Vancomycin inhibits cell wall synthesis by preventing the incorporation of N-acetyl muramic acid into the peptidoglycan of gram-positive bacteria. This causes cell wall destabilization and eventual cell wall lysis, killing the bacteria. Although vancomycin is considered bactericidal, its effects are blunted when there is a high inoculum of bacteria. [15] Studies have also shown β-lactam antibiotics are superior to vancomycin when treating serious methicillin sensitive S. aureus (MSSA) infections. [16, 17]
Vancomycin has minimal absorption when given orally and requires intravenous administration to treat systemic infections. [18] After administration, vancomycin exhibits complex concentration-time profiles which can be characterized by one-, two-, and three-compartment pharmacokinetic models. [4, 19, 20] Patients with normal renal function have an α-distribution phase of 0.5-1.0 hours, a β-elimination half-life of 6-12 hours and a volume of distribution of 0.4 – 1.0L/kg. [4, 18, 20] Renal clearance of unchanged drug accounts for 80-90% of vancomycin’s elimination. [18, 21] Initial studies estimated vancomycin was approximately 10% protein bound, but it is now widely accepted that levels of protein binding to albumin range from 50-55%. [22, 23]

Vancomycin distribution varies with the organ, state of inflammation and patient comorbidities. Penetration into the cerebrospinal fluid (CSF) can range from 0-18% in normal hosts, and can reach up to 48% in patients with inflamed meninges. [24] Patients with diabetes have significantly less vancomycin distribution to the skin and soft tissue compared to non-diabetic patients. [25] The ability of vancomycin to distribute into lung tissue also varies: in healthy volunteers, the penetration rate is reported to be about 50%, but may be 6-fold lower than serum concentrations in critically ill patients. [12]

*In vitro*, animal models, and human studies have shown AUC$_{24h}$:MIC is the preferred pharmacokinetic-pharmacodynamic parameter for vancomycin: increasing vancomycin concentrations did not enhance the effect in the bacterial kill curves. [22, 26][27] Serum concentrations 3-5 times the MIC optimize its antibacterial activity. [22, 26, 28-31]

In 2000, Moise et al. completed a retrospective study to determine treatment factors that were predictive of clinical and microbiological outcomes in patients with *S. aureus* pneumonia. Using classification and regression tree (CART) analysis, they identified AUC$_{24h}$:MIC breakpoints of >345mg*h/L and >866 mg*h/L correlated with a 78% clinical cure rate and a 91% microbiologic cure rate, respectively. [32] However, subsequent studies have reported a range of AUC$_{24h}$:MICs that may be required to achieve clinical cure, indicating there is still controversy for the optimal target. [33-38] Brown et al., found an AUC$_{24h}$ of >211 mg*h/L was associated with a 4-fold reduction in attributable mortality for patients with complicated bacteremia and endocarditis; Zelenitsky et al. determined an AUC$_{24h}$:MIC≥451mg*h/L and ≥578 mg*h/L correlated with increased rates of survival for MRSA-associated septic shock; and others have found AUC$_{24h}$
between these values. [36, 38] In a follow up to their previous study, Moise-Broder et al. sought to clarify the relationship between vancomycin dose, serum concentration, and MIC with treatment failure. In patients with *S. aureus* ventilator associated pneumonia, they found that clinical and bacteriological outcomes were superior in patients that achieved an AUC$_{24h}$:MIC$_{MIC}$≥400mg*h/L. [37] The results of this study were incorporated into the IDSA guidelines and extrapolated to other serious, deep-seated infections like infective endocarditis, and meningitis. [14]

1.4 Therapeutic drug monitoring

The correct monitoring parameters to optimize vancomycin efficacy and minimize toxicity remain controversial, and the recommendations have been changed numerous times.

Early recommendations were not based on any pharmacokinetic-pharmacodynamic studies and recommended targeting a peak serum concentration of 30-40mg/L to optimize efficacy and a trough of 5-10mg/L to minimize nephrotoxicity. [14] A literature review by Cantu et al. identified 167 patients who experienced vancomycin-related toxicity. [39] He was not able to identify any cases where vancomycin caused nephrotoxicity when used alone nor was he able to find any evidence supporting maintaining serum vancomycin levels within a certain range to minimize toxicities. He questioned the utility of performing therapeutic drug monitoring for vancomycin, citing increased costs with no improvement in safety or efficacy. Instead, he recommended considering a patient’s age, weight and renal function to determine “safe and effective vancomycin dosage regimens.” [39]

Based on the previously mentioned work by Moise-Broder et al. in 2004, the guidelines supported the use of the target AUC$_{24h}$:MIC$_{MIC}$≥400mg*h/L. [14, 37] For an average 80kg patient with normal renal function (creatinine clearance [CrCl] >100mL/min) receiving the standard vancomycin dose of 1g every 12 hours, an AUC$_{24h}$ of approximately 250mg*h/L would be predicted, based on estimates using the Rodvold nomogram. [4] However, this dosing regimen would only achieve the desired AUC$_{24h}$:MIC$_{MIC}$≥400mg*h/L if the pathogen had an MIC<0.5mg/L. Since an AUC$_{24h}$ of 250mg*h/L was typically associated with a steady state trough of 10mg/L, a target trough of 15-20mg/L was proposed in order to achieve the target AUC$_{24h}$:MIC for pathogens with an MIC of 1mg/L. [14, 37]
Following the work of Moise-Broder et al. and recommendations to maintain troughs of 15-20mg/L for deep-seated infections, there were a series of studies that assessed the relationship between serum vancomycin trough and clinical and safety outcomes. The first study by Jeffres et al. evaluated the effect of target serum vancomycin trough concentrations of 15-20mg/L on clinical outcome in patients with MRSA pneumonia. They found there was no difference in mean vancomycin trough or mean calculated AUC$_{24h}$ between survivors and non-survivors. [40]

Hidayat et al. conducted a prospective cohort study of adult patients to determine the effects of pathogen vancomycin MIC on treatment outcomes: clinical response, mortality, and nephrotoxicity. Patients were assessed for nephrotoxicity based on whether they achieved a high trough ($\geq 15$mg/L) or low trough (<15mg/L). They found that only patients in the high trough group experienced nephrotoxicity and nephrotoxicity was predicted by the use of concomitant nephrotoxic agents. There were lower rates of clinical response and infection related mortality in the high MIC group ($\geq 2$mg/L) versus the low MIC group (<2mg/L), though those in the high trough group had better clinical response.[41]

Lee-Such et al. performed a retrospective chart review of adult patients who received vancomycin for greater than 14 days and had a serum creatinine and Cockcroft-Gault calculated CrCl >30mL/min. Patients were assessed in two cohorts: low serum vancomycin trough ($\leq 15$mg/L) and high serum vancomycin trough (>15.1mg/L). The authors found that patients in the low trough serum vancomycin cohort had a median increase in serum creatinine of 0% with a frequency of nephrotoxicity of 0% compared to patients in the high trough serum vancomycin concentration cohort who experienced a median maximum serum vancomycin concentration of 17.2mg/L and frequency of nephrotoxicity of 15%. However, the authors indicated they were unable to determine whether the higher serum vancomycin levels were the cause or the result of worsening renal function. [42]

In addition to Hidayat et al., there have been two studies that have shown that targeting higher troughs (>15mg/L) lead to improved patient outcomes. [41] Zelenitsky et al. looked at critically ill patients with MRSA associated septic shock and found survival was 2.5 times higher in patients with a trough >15mg/L. [38] Kullar et al. completed a retrospective cohort study and completed a logistic regression to identify infective endocarditis, nosocomial-acquired infection,
initial vancomycin trough <15mg/L, and pathogen MIC>1mg/L as independent predictors of treatment failure. [36]

Although the IDSA guidelines recommend targeting vancomycin serum troughs of 15-20mg/L, studies have shown achieving these target troughs does not always correlate with efficacy and can increase the risk of nephrotoxicity. Therefore, alternate monitoring strategies should be investigated to improve and optimize the safety and efficacy of vancomycin.

1.5 Vancomycin associated nephrotoxicity

Vancomycin associated nephrotoxicity (VAN) has been a concern since it was first marketed in the 1950s, but the extent to which vancomycin is truly nephrotoxic has also been the centre of numerous debates. Impurities in the initial formulation and concomitant use of aminoglycosides were thought have contributed to the nephrotoxicity seen in early studies. As the purity of vancomycin formulations increased, the incidence of adverse events decreased. [43, 44] The incidence of VAN can be as low as 0% in the absence of other nephrotoxic agents and as high as 40%. [14]

The exact mechanism of nephrotoxicity is not completely understood. [14] Vancomycin can cause dose-dependent proliferation of proximal tubular cells, stimulating oxidative phosphorylation, producing free oxygen radicals. [45, 46] The free oxygen radicals then depolarize mitochondrial membranes, releasing caspase-3, which is known to be involved with apoptosis and may potentially cause proximal tubular necrosis. [47] Animal model studies have shown that antioxidants may be protective against vancomycin-induced renal injury by inhibiting the production of free oxygen radicals. [48] Concomitant use of vancomycin with aminoglycosides results in a risk of nephrotoxicity that is higher than either agent alone, perhaps because both agents generate reactive oxygen species [45, 46, 49, 50]; although the exact mechanism is poorly understood.

Several risk factors have been implicated in the development of VAN: total daily vancomycin dose, vancomycin AUC$_{24hr}$, duration of therapy, patient demographics, severity of illness, and concurrent nephrotoxin use. [9, 40, 41, 51-66] Development of VAN has been associated with increased mortality, and increased duration of both intensive care unit (ICU) and hospital length of stay. [36, 67]
A retrospective study by Lodise et al. compared the rates of nephrotoxicity in patients receiving high dose vancomycin (≥4g daily), standard dose vancomycin (<4g daily), and linezolid. They found a significant difference in the rates of nephrotoxicity between the three groups (34.6%, 10.9%, and 6.7%, respectively; P=0.001). Logistic regression identified patients receiving high dose vancomycin had a vancomycin associated nephrotoxicity odds ratio (OR) of 4.4. [60]

The relationship between vancomycin AUC_{24h} and VAN has not been widely studied. Lodise et al. used CART analysis on 166 patients and found an AUC breakpoint of 1300mg*h/L. Vancomycin associated nephrotoxicity was found in 26% of patients above and 10% of patients below the breakpoint. [61] More recent studies by Chavada et al. [51] and Zasowski et al. [66] have identified an AUC_{24h} CART analysis breakpoint of 563mg*h/L and 700mg*h/L, respectively.

VAN has been reported as early as 2-3 days after beginning therapy; however, the risk increases with increased duration of therapy and VAN is not usually seen until at least 4-8 days of therapy. [41, 58, 65] There are positive associations with longer courses of vancomycin, including >7 days, [64]>14 days, [40] and >15 days. [56] Two studies have found varying increases in the OR for VAN for every additional day the patient receives vancomycin. [68, 69] VAN is reversible with complete recovery of renal function in most patients within 7 days, even when vancomycin was continued. [40, 61, 64] Temporary dialysis may be needed with VAN in up to about 3% of patients. [70]

Most patient demographics have not been found to be associated with VAN with the main exception being increased age. [56] The other patient demographic that remains controversial is obesity. [52, 56, 60] Dosing vancomycin based on actual body weight, as recommended by guidelines, can result in total daily doses ≥4g. While some studies identified total body weight ≥100kg was associated with vancomycin associated nephrotoxicity using multivariable analysis, other studies have not. [52, 56, 60]

Severity of illness can impact the development of VAN. Patients who are critically ill can have numerous other reasons for developing an acute kidney injury; such as sepsis, radiocontrast exposure, hemodynamic instability, and concomitant use of other nephrotoxic agents. Numerous studies have identified Acute Physiology and Chronic Health Evaluation (APACHE II score, [52, 53]Charlson Comorbidity Index, [62]Sequential Organ Failure assessment, [69]or stay in the
ICU [60, 61, 67] as independent risk factors for developing acute kidney injury in patients receiving vancomycin. Other comorbid conditions that have been associated with nephrotoxicity include hypotension, [62] heart failure, [71] cancer, [67] renal dysfunction, [41, 67, 71] and previous acute kidney injury. [67]

Debate also exists regarding an enhanced risk of nephrotoxicity when vancomycin is used concurrently with aminoglycosides. [8, 72-76] Rybak et al. found patients receiving both vancomycin and an aminoglycoside were 6.7 times more likely to develop nephrotoxicity than patients who received vancomycin alone. [9] Most studies have found a 3- to 4-fold increase in the risk of developing nephrotoxicity when combination vancomycin and aminoglycoside therapy is used, but other studies did not identify an additive nephrotoxic effect. [8, 14, 73]

Since the early 2010s, there has been growing interest in the nephrotoxic potential of combination therapy of piperacillin-tazobactam with vancomycin. Numerous studies identified a higher risk of AKI in patients receiving piperacillin-tazobactam in combination with vancomycin versus monotherapy with acute kidney injury (AKI) vancomycin. [54, 55, 59, 62] However, studies by Moenster et al. and Hammond et al. failed to detect a significant difference in the incidence of AKI in patients receiving vancomycin with piperacillin-tazobactam versus those receiving vancomycin with cefepime. [57, 63]

1.6 Other Vancomycin toxicities

Other, less common vancomycin toxicities include ototoxicity, rash, red man syndrome, and various hematologic effects including neutropenia and thrombocytopenia. [77-80]

Causation between vancomycin and ototoxicity is unclear. Some reports implicate that vancomycin-induced ototoxicity is due to damage to the auditory nerve that initially affects the high-frequency sensory hairs in the cochlea followed by the middle- and low-frequency hairs, potentially leading to total hearing loss; similar to the mechanism associated with aminoglycosides. [14, 81] Reversible tinnitus with or without high-tone deafness has also been reported. [14] However, the exact role of vancomycin causing ototoxicity is not clearly defined. Reviews of cases of vancomycin associated ototoxicity identified concomitant use of other ototoxic agents, such as aminoglycosides, or use of the early, impure formulations of vancomycin as potential alternative causes. Researchers have also failed to identify a correlation
between vancomycin serum peak or trough concentrations and ototoxicity. A more recent retrospective study found patients receiving vancomycin where the trough target was 10-20mg/L were at increased risk of developing ototoxicity if they were >53 years old. [82] However, the authors were cautious in interpreting their results given the small sample size and retrospective design. Thus, the risk of developing ototoxicity when vancomycin monotherapy is used is considered to be low. [14]

The incidence of red man syndrome is 3.7-42% in infected patients. [77] Red man syndrome occurs when doses are infused rapidly, resulting in histamine release from cutaneous mast cells which can cause tingling and flushing of the face, neck, and upper torso. [83] Prolonging the infusion time or premedicating with diphenhydramine minimizes the potential of developing red man syndrome. Red man syndrome is considered a pseudo-allergy because it is caused by the release of histamine from cutaneous mast cells and not an underlying immune process. [84]

Vancomycin induced neutropenia is defined as an absolute neutrophil count <1000cells/µL and the reported rates range from 2 to 12%. [8, 85, 86] A review by Black et al. found the biggest predictor of developing neutropenia was vancomycin vancomycin duration of therapy greater than 7 days. [78] There are also limited reports of vancomycin induced thrombocytopenia. A review of 29 patients receiving vancomycin who developed thrombocytopenia identified vancomycin-induced autoantibodies as the potential cause. [79]

1.7 Challenges with current dosing and monitoring recommendations

Unfortunately, the guideline recommended dosing for IIV of 15mg/kg every 12 hours is unlikely to achieve the target vancomycin trough concentrations of 15-20mg/L in patients with normal renal function. [20, 21, 43, 87-92]

The initial vancomycin dose nomogram by Matzke et al. was published in 1984 and sought to characterize vancomycin pharmacokinetics in 56 patients with varying renal function. [20] The authors observed a relationship between the vancomycin serum clearance and creatinine clearance which they used to develop a nomogram for initial and maintenance dosing of vancomycin. Unfortunately, the nomogram recommendations of a 25mg/kg loading dose followed by 19mg/kg every dose interval were designed to achieve a trough of 7.5mg/L [20],
half the recommended target trough recommended for serious infections by the published guidelines. [14]

In a study by Drusano et al., pharmacokinetic data from 21 patients receiving vancomycin who had measured CrCl was used to simulate vancomycin trough concentrations in patients with a CrCl of 40, 60, 80, and 100mL/min. [88] The results of this study showed that patients who received 15mg/kg of vancomycin every 12 hours had a probability of target trough attainment of 15.7%, 14.0%, 10.6%, and 7.4%, respectively, with a CrCl of 40, 60, 80, and 100mL/min. Thus, they concluded the need to identify alternative dosing regimens to achieve effective and non-toxic drug exposure with vancomycin and highlighted the need for therapeutic drug monitoring to ensure therapeutic targets are achieved.

Chung et al. performed a prospective cohort study to determine the optimal vancomycin dose required to achieve therapeutic levels in critically ill patients with Staphylococcus aureus pneumonia. [87] Patients received 1g every 12 hours if their CrCl>60mL/min, 1g every 24-48 hours if their CrCl 30-60mL/min, 1g every 72-96 hours if their CrCl<30mL/min. Vancomycin troughs were taken 30min prior to the next dose and optimal doses were calculated to achieve an end of dosing interval trough of 15-20mg/L. Across all the empiric standard dosing regimens based on CrCl used in this study, only 23.5% of patients were able to achieve target levels, 20.6% had trough concentrations ≥20mg/L, and 55.9% of patients achieved subtherapeutic troughs. Thus, the authors suggested the current vancomycin treatment guidelines may not be optimal in the patient population.

In response to sub therapeutic troughs, clinicians will often respond by using larger doses and/or more frequent administration. Unfortunately, this can result in the patient receiving total daily doses of ≥4g, which have been associated with an increased risk of nephrotoxicity. [61]

Although the guidelines proposed a vancomycin trough concentration of 15-20mg/L as a surrogate marker for attainment of an AUC_{24}:MIC≥400mg*h/L, the relationship is poor and may result in needless increases in dosing. [14, 32, 93] There has been increasing interest in the relationship between vancomycin serum trough concentration and AUC_{24h}:MIC.

In a study by Neely et al., Monte Carlo simulation was conducted to determine the probability of achieving an AUC_{24h}:MIC≥400 mg*h/L in adult patients with normal renal function. They found
that 60% of patients would achieve the desired $\text{AUC}_{24h}$ target with a trough <15mg/L. However, since $\text{AUC}_{24h}$ is difficult to measure in clinical practice with IIV and trough concentrations are used as a surrogate marker for $\text{AUC}_{24h}$, clinicians may increase the patient’s dose to achieve a trough of 15-20mg/L, thus potentially increasing the risk of VAN. [93]

Following this study, two groups conducted studies comparing AUC-guided dosing and traditional trough concentration-guided dosing. The study by Finch et al. [94] included 1280 patients. AUC-guided dosing was associated with lower rates of nephrotoxicity by both logistic regression and Cox proportional hazards regression. The AUC-guided dosing strategy was also associated with lower total daily doses, $\text{AUC}_{24h}$, and trough concentrations. [94]

In a follow-up prospective study conducted by Neely et al. [95] a BestDose Bayesian software tool was used to control vancomycin dosing. In the first year, clinicians targeted trough concentrations from 10-20mg/L, depending on the indication. In years 2 and 3, the study team used the software to achieve a steady state $\text{AUC}_{24h}$:MIC 400-800mg*h/L regardless of trough concentration. They found a significant decrease in the median trough concentration by year: 14.4, 9.7, and 10.9mg/L (P=0.005); decreased number of patients, 36%, 7%, and 6%, with troughs >15mg/L; and no difference in efficacy. [95]

### 1.8 Studies comparing intermittent infusion and continuous infusion vancomycin

One of the earliest studies assessing continuous infusion vancomycin was in 1995 by Wysocki et al. [96] The authors compared 13 patients prospectively given CIV, targeting a steady state concentration ($C_{ss}$) of 20-30mg/L, with historical controls and did not find any differences in their safety or efficacy outcomes. They followed up this study with the first and only randomized control trial in 2001, comparing CIV and IIV in ICU patients with severe MRSA infections. [97] A CIV $C_{ss}$ of 20-25mg/L was chosen based on current staphylococcal MIC data, protein binding, and the ability of vancomycin to penetrate into tissues. Patients receiving CIV were compared to patients receiving IIV with a target of 10-15mg/L. The two dose modalities were found to be comparable in clinical efficacy, microbiologic cure, and nephrotoxicity. CIV was found to achieve target concentration faster, require fewer serum samples to monitor treatment, had lower total daily doses, and lower patient level costs. [97]
Subsequent studies comparing IIV and CIV have targeted CIV steady state levels ranging from 15-25mg/L, but the target range was not justified. Patients enrolled in the studies achieved an average plateau of 20mg/L and did not appear to be at increased risk of developing vancomycin associated nephrotoxicity. Meta-analyses comparing CIV and IIV have shown there is no difference in clinical outcome or mortality, and potentially a benefit in nephrotoxicity. [98, 99]

With CIV, an increasing risk of nephrotoxicity has been observed with increasing C\textsubscript{ss} levels. [100-102] Ingram \textit{et al.} identified patients receiving CIV as an outpatient with a vancomycin C\textsubscript{ss}\geq28mg/L were 21 times more likely to experience vancomycin associated nephrotoxicity. [100] In addition, the risk of nephrotoxicity rose to greater than 20% when the C\textsubscript{ss} level was > 20mg/L. [100] Norton \textit{et al.} completed a similar study in outpatients and identified a C\textsubscript{ss}\geq32mg/L as an independent risk factor for developing vancomycin associated nephrotoxicity. [101] However, it is important to note that there is data to support that outpatients were observed to be at lower risk of developing vancomycin associated nephrotoxicity because they were less likely to experience other forms of renal injury including surgery, sepsis, and exposure to other nephrotoxic agents like radiocontrast. [100]

Spapen \textit{et al.} conducted a retrospective evaluation of vancomycin associated nephrotoxicity in critically ill patients receiving CIV, targeting a C\textsubscript{ss} 15-25mg/L. [102] They found acute kidney injury developed in 29.5% of patients, and patients who developed AKI had higher body weight, were more likely to be diabetic, and required vasopressors. Vancomycin specific factors identified as contributing to the risk of AKI included longer treatment duration (14.9 vs 9.2 days; p=0.05) and a C\textsubscript{ss}\geq30mg/L.

A summary of studies that looked at CIV can be seen in (adapted with permission from. [103]).

As mentioned by Wysocki \textit{et al.}, other potential benefits of CIV over IIV include: faster attainment of therapeutic levels, less variability, fewer serum samples to monitor treatment, lower total daily doses, and lower patient level costs. [97] Lin \textit{et al.} found for patients receiving continuous veno-venous hemofiltration, all patients who received CIV were able to attain target levels within 24 hours compared to only 4% (2/45) of patients who received IIV. [104]

Therefore, dosing with CIV may allow attainment of a 12-20mg/L C\textsubscript{ss} target while limiting the total daily vancomycin dose compared to IIV dosing targeting a trough of 12-20mg/L. As a
result, CTV may be beneficial in reducing the risk of nephrotoxicity in those patients whose calculated IIV dosing is $\geq 4g$/day (e.g. young patients with good renal function, critically ill hyperdynamic patients, burn patients, obese patients).
<table>
<thead>
<tr>
<th>First Author, Reference</th>
<th>Study Design</th>
<th>Patient Population</th>
<th>Sample Size</th>
<th>Dosing Strategies</th>
<th>Cs Vancomycin Targets (Justification of target)</th>
</tr>
</thead>
</table>
| Akers, KS[105]         | Retrospective comparative cohort | Burn ICU<sup>1</sup> | CIV: 90  
IIV: 81 | CIV: Observed mean dose of 29.5 ± 11.8mg/kg/day  
IIV: Observed mean dose of 26.2 ± 8.6mg/kg/day | 20-25mg/L ([97]) |
| Albanese, J[24]        | Prospective case series to characterize PK<sup>2</sup> | ICU: mechanical ventilation | CIV: 13  
LD<sup>3</sup>: 15mg/kg  
MD<sup>4</sup>: 50-60mg/kg/day | 20-30mg/L (not justified) |
| Bernand, E[106]        | Prospective case series | Gram-positive bone and joint infections | CIV: 15  
MD: 40mg/kg/day | 25-35mg/L (not justified) |
| Boffi el Amari, E[107] | Retrospective comparative cohort | Gram-positive osteomyelitis | CIV: 23  
IIV: 68 | MD: 40mg/kg/day | 20-25mg/L (not justified) |
| Byl, B [108]           | Prospective case series to compare and characterize PK | PK – uninfected pleural fluid exudates | CIV: 8  
IIV: 8 | CIV: LD: 500mg, MD: 30mg/kg/day  
IIV: 15mg/kg/day 2x/day | Mean: 16 ± 4.5mg/L (no given range targeted) |
| Cristallini, S[109]    | Prospective cohort | Adult septic patients | CIV: 107  
LD: 35mg/kg  
MD: CIV nomogram based on Cockcroft-Gault calculated CrCl | 20-30mg/L (target not justified) |
IIV: 14 | CIV: LD: 500mg,  
MD: 83mg/h  
IIV: 500mg 4x/day | NA |
| Hutschala, D[111]      | Retrospective comparative cohort | Cardio-surgical ICU | CIV: 119  
IIV: 30 | MD: 20mg/kg  
CIV: Observed mean dose 1935 ± 688mg/day  
IIV: Observed mean dose 1325 ± 603mg/day | 20-25mg/L based on MIC<sub>90</sub> for Staph spp., vancomycin protein binding and distribution |
<p>| Ingram, PR[100]        | Retrospective cohort | OPAT&lt;sup&gt;5&lt;/sup&gt; | CIV: 112 | LD: not reported | NA |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Comparator</th>
<th>Inclusion Criteria</th>
<th>CIV Dosing</th>
<th>IIV Dosing</th>
<th>MIC Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>James, JK [112]</td>
<td>Prospective randomized crossover study: 2 days of CIV or IIV then crossed over to receive the opposite regimen for 2 days</td>
<td>Suspected/ documented Gram-positive infection</td>
<td>10</td>
<td>CIV: LD: 500mg MD: 2000mg</td>
<td>IIV: MD: 1000mg every 12h</td>
<td>15mg/L (not justified)</td>
</tr>
<tr>
<td>Lin, H [104]</td>
<td>Retrospective comparative cohort</td>
<td>ICU on CVVH</td>
<td>CIV: 14</td>
<td>CIV: LD mean: 26.62 ± 3.06mg/kg, MD mean: 15.66 ± 6.26mg/kg/day</td>
<td>IIV: LD mean: 17.58 ± 5.72mg/kg, MD mean: 17.28 ± 4.96mg/kg</td>
<td>15-25mg/L (not justified)</td>
</tr>
<tr>
<td>Lin, H [113]</td>
<td>Retrospective comparative matched cohort</td>
<td>Obese vs non-obese SICU</td>
<td>26 matched pairs</td>
<td>LD: 25mg/kg MD: based on renal function</td>
<td>15-25mg/L (not justified)</td>
<td></td>
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<tr>
<td>Ng, TM [114]</td>
<td>Retrospective PK Model fitting plus prospective validation cohort</td>
<td>OPAT</td>
<td>Retrospective: 20 Prospective: 14</td>
<td>Discretion of MD</td>
<td>15-25mg/L (high likelihood of attaining AUC/MIC≥400 for most local MRSA isolates)</td>
<td></td>
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<tr>
<td>Norton, K [101]</td>
<td>Retrospective cohort</td>
<td>OPAT</td>
<td>CIV: 155</td>
<td>LD: up to 15mg/kg MD: not reported</td>
<td>20-30mg/L (not justified)</td>
<td></td>
</tr>
<tr>
<td>Oudin, C [115]</td>
<td>Retrospective cohort</td>
<td>Neonates</td>
<td>PK group: 68 Dosing group: 47</td>
<td>LD: 7mg/kg MD: 30mg/kg/day</td>
<td>10-30mg/L (not justified)</td>
<td></td>
</tr>
<tr>
<td>Payne, C [116]</td>
<td>Prospective observational</td>
<td>Vascular surgery prophylaxis</td>
<td>CIV: 21</td>
<td>LD: 1000-1500mg MD: based on renal function</td>
<td>10-25mg/L ([97], though target was different)</td>
<td></td>
</tr>
<tr>
<td>Author, Year</td>
<td>Study Design</td>
<td>Population</td>
<td>PK Approach</td>
<td>Dosing</td>
<td>Concentration Range</td>
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<tr>
<td>Pea, F [92, 117]</td>
<td>Retrospective observational PK characterization plus prospective validation</td>
<td>ICU</td>
<td>Retrospective: 70, Prospective: 63</td>
<td>LD: 15mg/kg, MD: nomogram based on CrCl</td>
<td>15-20mg/L (target not justified)</td>
<td></td>
</tr>
<tr>
<td>Roberts, JA [118]</td>
<td>Retrospective cohort PK modeling</td>
<td>ICU – septic patients</td>
<td>CIV: 206</td>
<td>LD: 35mg/kg, MD: 35mg/kg/day</td>
<td>20-25mg/L ([14], but there are no recommendations for CIV in guidelines)</td>
<td></td>
</tr>
<tr>
<td>Spapen, HD [102]</td>
<td>Retrospective cohort</td>
<td>Gram positive pneumonia and/or bacteremia</td>
<td>CIV: 129</td>
<td>LD: 15mg/kg, MD: 30mg/kg/day</td>
<td>15-25mg/L (not justified)</td>
<td></td>
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<tr>
<td>Van Maarseveen, EM [119]</td>
<td>Retrospective comparative cohort</td>
<td>ICU</td>
<td>CIV: 44, IIV: 27</td>
<td>CIV: LD: 1000mg, MD: nomogram based on renal function, IIV: Not reported</td>
<td>15-20mg/L (not justified)</td>
<td></td>
</tr>
<tr>
<td>Verrall, AJ [120]</td>
<td>Prospective comparative cohort study</td>
<td>OPAT MRSA infections</td>
<td>CIV: 188, IIV: 56</td>
<td>NA: only indicated weight based dosing</td>
<td>15-25mg/L (not justified)</td>
<td></td>
</tr>
<tr>
<td>Vuagnat, A [121]</td>
<td>Prospective comparative cohort study</td>
<td>Medical/Surgical Ward osteomyelitis</td>
<td>CIV: 23, IIV: 21</td>
<td>CIV: LD: 20mg/kg, MD: 40mg/kg/day, IIV: LD: 20mg/kg, MD: 20mg/kg every 12h</td>
<td>20-25mg/L (not justified)</td>
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<tr>
<td>Wysocki, M [96]</td>
<td>Prospective comparative cohort</td>
<td>ICU bacteremia/pneumonia</td>
<td>CIV: 13, IIV: 13</td>
<td>CIV: LD: 15mg/kg</td>
<td>20-30mg/L (maintain concentration 8-10x MIC)</td>
<td></td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Setting</td>
<td>CIV</td>
<td>CIV</td>
<td>With estimate of 55% protein binding</td>
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<tr>
<td>Wysocki, M [97]</td>
<td>Prospective RCT&lt;sup&gt;5&lt;/sup&gt;</td>
<td>ICU hospital acquired pneumonia</td>
<td>CIV: 61</td>
<td>CIV:</td>
<td>20-25mg/L (Consensus, available data for MRSA MIC, protein binding, and tissue distribution)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>IIV: 58</td>
<td>LD: 15mg/kg</td>
<td>MD: 30mg/kg/day</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>MD: 15mg/kg every 12h</td>
<td>MD: 15mg/kg every 12h</td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup>: ICU = Intensive care unit  
<sup>2</sup>: PK = Pharmacokinetic  
<sup>3</sup>: LD = Loading dose  
<sup>4</sup>: MD = Maintenance dose  
<sup>5</sup>: OPAT = Outpatient Antibiotic Therapy  
<sup>6</sup>: CVVH = Continuous Veno-Venous Hemodialysis  
<sup>7</sup>: SICU = Surgical Intensive Care Unit  
<sup>8</sup>: RCT = Randomized Control Trial
1.9 Rationale for continuous infusion vancomycin

Continuous infusion may be rational for certain antibiotics, such as vancomycin, that have time dependent killing in order to maximize the time that the concentration remains above the MIC while also minimizing total drug exposure. Since vancomycin is 50% protein bound and only unbound drug is pharmacologically active, serum concentrations of 10mg/L and 20mg/L would be necessary to maintain levels 5 times above an MIC breakpoint of 1 and 2mg/L, respectively. With CIV, AUC$_{24h}$ can be easily determined as the product of C$_{ss}$ * 24 hours. In order to achieve an AUC$_{24h}$:MIC>400mg*h/L for a pathogen with a vancomycin MIC breakpoint of 1mg/L, a patient would require a C$_{ss}$ ≥16.7mg/L. Therefore, targeting a C$_{ss}$ between 15-20mg/L may be considered reasonable for efficacy and safety. [44, 92, 104, 117, 119, 122-124] In patients with gram positive bacterial infections with borderline vancomycin susceptibility (MIC 1.5-2.0mg/L), CIV may be able to attain target AUC$_{24h}$:MIC≥350 or 400mg*h/L with lower daily doses than those needed with IIV, thereby potentially reducing the risk of nephrotoxicity.

Patients requiring outpatient antibiotic therapy may benefit from receiving CIV because they can have levels drawn at any time without the need to coordinate the timing of the blood draws at the lab with the time for administration of the next dose by the home care nurse. Clinicians will be able to easily interpret the level and then make dose adjustments by proportion if necessary. Conversely, clinicians may have difficulty interpreting supratherapeutic troughs for patients receiving IIV because they may not be able to tell if the trough is truly elevated or if the patient had a level drawn too early; thus increasing the complexity, appropriateness and accuracy of making vancomycin dose adjustments.

Finally, CIV may have a reduced cost compared to IIV due to a reduced total daily dose; and decreased number of vancomycin daily prepared doses, vancomycin serum concentration samples required to monitor therapy, number of orders for blood work, and time required for a clinician to do initial consultation and follow-up evaluations. [97, 104, 125]

1.10 Sunnybrook Health Sciences Centre Experience with Continuous Infusion Vancomycin

The main sites for this study, Bayview, Holland, and St. John’s Campuses of Sunnybrook Health Sciences Centre (SHSC), use IIV as the standard modality with a target trough of 15-20mg/L in
patients with complicated infections (e.g. MRSA pneumonia, endocarditis, meningitis, and osteomyelitis). Since 2012, the Infectious Diseases Consult Service at SHSC Bayview and Holland Campuses have been using continuous infusion vancomycin in select hospitalized patients and outpatients. At these campuses, patients are eligible to receive continuous infusion vancomycin if their calculated total daily IIV dose is ≥4g (e.g. young otherwise healthy patients, critically ill hyperdynamic patients, and obese patients). [60] In addition, inpatients and outpatients from these campuses may also be eligible to receive CIV if they require prolonged courses of vancomycin (>14 days). To date, there have been no internal reports indicating CIV has increased risk of vancomycin associated nephrotoxicity or clinical failure compared to IIV.

1.11 Study Rationale

Although CIV is not a new concept, there is renewed interest in this dosing modality with evidence for at least equal efficacy and safety. [24, 44, 69, 97, 100, 101, 104-109, 111-114, 116, 118-123, 126-137] However, there are many unanswered questions with the use of CIV. One gap in the literature is the comparison of efficacy and safety of CIV versus IIV where both regimens target a concentration of 12-20mg/L ($C_{ss}$ or trough, respectively).

The target steady state vancomycin trough or random level varied depending on the attending clinician, indication, and pathogen. Unfortunately, the target steady state $C_{ss}$ or trough was not always clearly documented in the paper chart or EPR. Since the majority of the infections were coagulase-negative $Staphylococci$ (CNST) prosthetic joint infections (PJI), where clinicians may have chosen to target lower trough concentrations, the target range for serum vancomycin trough or steady state concentration used in this study was defined as 12-20mg/L.

1.12 Study Objectives

1.12.1 Primary Research Question

- In adult inpatients with a documented or presumed Gram-positive bacterial infection, is there a difference in vancomycin associated nephrotoxicity, as defined by the RIFLE criteria [1] (Appendix 1), between patients receiving continuous infusion vancomycin and intermittent infusion vancomycin?
1.12.2 Secondary Research Questions

- Is there a difference in clinical and microbiological outcomes with CIV compared to IIV?
- Is there a difference in total daily vancomycin dose for patients receiving CIV compared to IIV?
- Is CIV associated with a shorter time to attain therapeutic levels compared to IIV?
- Is CIV associated with a greater likelihood to achieve target levels with the final daily dose compared to IIV?
- Is there a difference in the number of dose adjustments with CIV compared to IIV?
- Is there a difference in the number of vancomycin levels ordered with CIV compared to IIV?
- Is there a difference in the incidence of other, non-nephrotoxic vancomycin adverse effects with CIV compared to IIV?

1.13 Study hypothesis

In this multicentre, retrospective cohort study, we hypothesized that CIV had a lower risk of vancomycin associated nephrotoxicity compared to IIV while maintaining comparable rates of clinical cure and microbiological cure; with a lower total daily dose required to achieve therapeutic levels, fewer number of days to target level attainment, less frequent monitoring, and fewer dose adjustments.

The null hypothesis for the primary objective of the study was that there was no difference in vancomycin associated nephrotoxicity between CIV and IIV.
Chapter 2

METHODS
2 Methods

2.1 Study Setting

The study was performed at the Bayview, Holland Centre, and St. John’s Rehab Campuses of Sunnybrook Health Sciences Centre and the Michael Garron Hospital (formerly Toronto East General Hospital) of the Toronto East Health Network.

2.1.1 Sunnybrook Health Sciences Centre Sites

Sunnybrook Health Sciences Centre (SHSC) is located in Toronto, Ontario, Canada, and has three sites: Bayview campus, Holland Orthopaedic and Arthritic Centre, and St. John’s Rehab. The SHSC Bayview campus (SHSC-BC) is a 1325-bed adult teaching hospital with acute care facilities and adjoining veteran’s long-term complex care facility. Programs include neurosciences; oncology; cardiovascular diseases; trauma, emergency and critical care; veterans and community; and women and babies. SHSC-BC has three level III intensive care units (ICUs) (critical care unit, cardiovascular surgery intensive care unit, Ross Tilley Burn Centre); and three level II ICUs (Coronary Intensive Care Unit, Neurosurgical Intensive Care Unit, and Medical Stepdown Intensive Care Unit).

The SHSC Holland Orthopaedic and Arthritic Centre (SHSC-HOAC) is a 62-bed facility that specializes in traumatic injury management; joint reconstruction and replacement; complex upper and lower limb surgery; sports related injury management; rehabilitation; and rheumatology.

St. John’s Rehab hospital (SJR) is a 160 bed facility that provides rehabilitation programs for patients recovering from amputations, traumatic injuries, burns, cardiovascular surgery, strokes, transplants, cancer, and complex neurological and orthopaedic conditions.

2.1.2 Michael Garron Hospital

The Michael Garron Hospital (MGH) is a 515-bed urban community teaching hospital located in Toronto, Ontario, Canada, with programs including complex continuing care and short-term rehabilitation, women and babies, paediatrics, and mental health.
2.2 Population of interest

2.2.1 Patients Eligible for Inclusion

All adult (aged ≥ 18 years) inpatients and infectious diseases consult service outpatients prescribed vancomycin by continuous infusion vancomycin (CIV) or intermittent infusion vancomycin (IIV) between January 1st, 2010 and December 31st, 2016. Patients were recruited from SHSC-BC, SHSC-HOAC, SHSC-SJR, and MGH.

2.2.1.1 Patient Inclusion Criteria

Patients were eligible for inclusion if:

1. They received a minimum of 48 hours of intravenous vancomycin and continued based on culture results; and

2. There was a minimum of one steady state vancomycin concentration (i.e. trough concentration obtained immediately prior to the 3\textsuperscript{rd} maintenance dose for ≥ every 12 hour dosing; prior to the 4\textsuperscript{th} dose for ≤ every 8 hour dosing of IIV; or a random steady state concentration [C\textsubscript{ss}] obtained at least 24 hours after initiation of CIV); [18]and

Patient eligibility for inclusion was based on satisfaction of all study inclusion criteria during their first admission and course of vancomycin related to a specific surgical procedure or diagnosis.

2.2.1.2 Patient Exclusion Criteria

Patients were excluded if they started on vancomycin at another institution or required any form of renal replacement therapy (e.g. peritoneal dialysis, intermittent hemodialysis, continuous renal replacement therapy) prior to initiating vancomycin.

2.3 Study Design

This was a retrospective, multicentre matched cohort study.
2.3.1 Patient identification

Eligible inpatients from the SHSC-BC were identified with the Stewardship Program Integrating Resource Information Technology (SPIRIT) database of the SHSC Antimicrobial Stewardship Program[139], which was used to query and generate a list of inpatients at SHSC-BC between March 12th, 2010 and December 31, 2016, inclusive. Additional eligible inpatients from SHSC-BC from January 1, 2010 to March 11, 2010 were identified using the pharmacy system WORx. Eligible outpatients from the SHSC-BC were identified from the SPIRIT database querying patients who remained on vancomycin at discharge. Eligible inpatients and outpatients from the SHSC-HOAC and the MGH from January 1, 2010 to December 31, 2016 were identified by the pharmacy systems, WORx and Cerner Powerchart, respectively, and the collaborating physicians at these sites. Eligible patients at SHSC-SJR were initially identified as SHSC-BC patients who were subsequently transferred to SHSC-SJR for inpatient rehabilitation. Sources of patient data for extraction included SPIRIT (SHSC-BC) and pharmacy systems (SHSC-HOAC and MGH), electronic patient records (EPR/Sunnycare at SHSC-BC or SHSC-HOAC and Cerner Powerchart at MGH) and hospital charts (all sites).

2.3.2 Data extraction

Firstly, patients receiving CIV were identified from the list of eligible patients. Data collection was completed between May 2017 and May 2018. The following information was extracted into a Microsoft Excel file: hospital file number (HFN); date of admission (DOA); date of discharge (DOD); hospital site of vancomycin initiation (SHSC-BC, SHSC-HOAC, or MGH); hospital location of vancomycin initiation (ward versus ICU); vancomycin start and stop date; severity of illness score (Pitt bacteremia score for ward patients, APACHE II score for ICU patients); initial vancomycin dose and frequency; date of initial vancomycin level; initial vancomycin steady state trough concentration with IIV or $C_{ss}$ with CIV; vancomycin dosing adjustments made subsequent to vancomycin serum concentration(s) (yes/no); number of vancomycin dosing adjustments until target levels attained; final steady state trough concentration or $C_{ss}$; initial and final vancomycin daily dose; number of vancomycin levels ordered; any positive cultures (date ordered, source, culture, susceptibility); other concomitant antibiotics used during vancomycin therapy (antimicrobial name, start date, and stop date); concomitant infection(s) for which concomitant antibiotics were being used (if different than the infection for which vancomycin was indicated); concomitant nephrotoxins, ototoxins and drugs known to cause acute interstitial nephritis.
(Appendix 5.2); and outcome data (clinical cure, microbiological cure, and mortality) on date of vancomycin completion and up to 14 days after completion of vancomycin (Section 2.4).

2.3.3 Patient matching

Once data collection was completed for all CIV patients, they were matched at a 1:1 ratio to eligible patients receiving IIV based on as many of the following factors as possible:

- Hospital admission location (inpatient ward versus critical care unit, with admission or transfer to a critical care bed within 48 hours of vancomycin initiation classified as hospital location in a critical care unit; and hospital site: SHSC-BC, SHSC-HC, MGH);
- Sex;
- Age (+/- 5 years);
- Duration of therapy (< 7 days, 7-14 days, 15-21 days, 22-90 days, > 90 days);
- Infection related diagnosis; pathogen(s) cultured (Gram-positive only, polymicrobial [concomitant Gram-negative, fungal, and/or viral], or culture negative);
- Existence of comorbidities (congestive heart failure [CHF], chronic obstructive pulmonary disease [COPD], diabetes mellitus [DM], drug or disease related immunosuppression);
- Severity of illness (APACHE II score for ICU patients, and Pitt bacteremia score for ward patients [2, 140]);
- Concomitant nephrotoxins (Yes/No) (Appendix 2);
- Concomitant ototoxins (Yes/No) (Appendix 2);
- Baseline creatinine clearance (CrCl) (+/- 25mL/min) or baseline serum creatinine (sCr) (+/- 25µmol/mL);
- Length of stay at vancomycin initiation (0-2, 3-7, 8-14, 15-21, 22-90, >90 days);
- Concomitant rifampin therapy;
- Month (+/- 30 days) and year (+/- 1 year) of initiating vancomycin; and
- Baseline weight (+/- 10kg).

Although the Pitt Bacteremia score has only been validated as a measure of severity of infection in bacteremic patients, it was used as a measure of severity of illness in all hospital ward patients, as there are no other validated measures of severity of illness in these patients. [140]
Recognizing that it was not possible to match for all factors, priority matching of factors was based on the order of appearance of the factors in the aforementioned relevant sentence above.

2.3.4 Data sources

Eligible inpatients from the SHSC-BC were identified with the Stewardship Program Integrating Resource Information Technology (SPIRIT) database of the SHSC Antimicrobial Stewardship Program. [139]

Eligible inpatients from SHSC-HOAC, SHSC-SJR, and MGH were identified using the pharmacy systems and collaborating physicians at the sites. Sources of patient data for extraction included SPIRIT (SHSC-BC), pharmacy systems (SHSC-HOAC, SHSC-SJR, and MGH), electronic patient records (EPR/SunnyCare at SHSC-BC or SHSC-HOAC and Cerner Powerchart at MGH), and hospital charts (all sites).

2.4 Outcome definitions

2.4.1 Primary outcome

Vancomycin associated nephrotoxicity was defined as either:

1. RIFLE criteria of nephrototoxic risk or renal injury were met (Appendix 1) [1], as determined by the maximum serum creatinine value during a course of vancomycin obtained any time from 48 hours after initiation of vancomycin therapy and up to 14 days after discontinuing vancomycin; or

2. If the patient required any form of renal replacement therapy (RRT) (e.g. intermittent hemodialysis, continuous renal replacement therapy, or slow low efficiency dialysis) at any point during vancomycin therapy or up to 2 weeks after completion of therapy.

2.4.2 Secondary outcomes

2.4.2.1 Clinical cure

Patients were only assessed for clinical cure if they had a documented Gram-positive infection for which vancomycin was indicated. Those with culture negative or concomitant Gram-negative bacterial, acid-fast bacilli, fungal, or viral infections were excluded. Additional exclusion criteria
for efficacy outcome included discharge to a non-study site facility, desensitization and completion of course with alternative antibacterial agent, if the patient chose an alternative therapy, or if the family chose to withdraw care. Patients were excluded from clinical cure assessment if they discontinued vancomycin due to non-renal toxicities.

Clinical failure was defined as any of the following:

- Death; or
- Readmission within 14 days of discharge for infection recurrence; or
- Initiation of a new antibiotic therapy with similar spectrum to vancomycin due to lack of response to vancomycin assessed by clinical signs and symptoms, laboratory values, or chart documentation for a culture proven sensitive pathogen (Appendix 5.2); or
- Either clinical or microbiological evidence of continued infection following second stage revision of a prosthetic joint.

Clinical cure was determined by chart documentation of resolution or documentation of resolution of the patient’s presenting signs and symptoms. If no clear presenting signs and symptoms were documented, then clinical cure was assessed by resolution of any general systemic signs of infection that were present at the time of diagnosis: hyper/hypothermia (>38°C or <36°C, respectively); tachycardia (heart rate >90 beats/min); tachypnea (respiratory rate >20 breaths/min); elevated white blood cell count ([WBC]; >10x10⁹ cells/L).

For patients who were on vancomycin for a two stage revision, clinical or microbiological cure was assessed based on outcomes from the final surgical procedure.

### 2.4.2.2 Survival

Attributable mortality was defined as chart documented mortality due to infection, including but not limited to: sepsis, septic shock, endocarditis, or meningitis. Non-attributable mortality was defined as mortality due to other causes during treatment and up to 30 days after discontinuing vancomycin.

### 2.4.2.3 Microbiologic outcomes

Microbiological success was defined as documented negative culture(s) during or up to 14 days after discontinuing vancomycin after an initial positive culture. Patients undergoing a two-step
prosthetic joint infection had microbiological cure assessed based on cultures taken from the second stage revision. Patients who did not have any repeat cultures during their course of vancomycin or up to 14 days after discontinuing vancomycin were excluded from assessment of microbiologic outcomes.

2.4.2.4 Theoretical difference in predicted IIV dose and actual CIV dose

For patients converted to CIV, the theoretical IIV dose they would have required to achieve a final steady state trough of 12mg/L was calculated. First, patients initially receiving IIV and later converted to CIV were identified. The theoretical final IIV dose to achieve a trough of 12mg/L was determined from individualized pharmacokinetic calculations with steady state peak and trough concentrations obtained prior to the switch to CIV when available; or calculated by proportion when only a steady state serum vancomycin trough was available prior to the switch to CIV. The theoretical IIV dose was then compared to the final CIV dose the patients required.

Example calculation:

\[
\frac{\text{Initial trough}}{\text{Initial total daily dose}} = \frac{\text{Desired trough}}{\text{Predicted total daily dose}}
\]

\[
\frac{7.34 \text{mg/L}}{2000 \text{mg/day}} = \frac{15 \text{mg/L}}{\text{Predicted total daily dose}}
\]

\[
\text{Predicted total daily dose} = 4087 \text{mg/day}
\]

2.4.2.5 Attainment of target steady state concentration and steady state trough 12-20mg/L

The target vancomycin steady state trough or \(C_{ss}\) for this study was defined as 12-20mg/L, with the rationale stated above in 1.11.

Attainment of target concentrations was assessed and assigned to the dose modality the patient was receiving when they achieved therapeutic levels. If a patient was started on IIV and did not achieve a steady state trough of 12-20mg/L, but achieved target levels after conversion to CIV, then the attainment of target concentrations for that course would be assessed as a failure for IIV and success for CIV. Those who did not achieve therapeutic concentrations on either IIV or CIV
were considered failures for both. Therefore, the total number of courses assessed may exceed the actual total number of courses as some courses would be assessed in both IIV and CIV.

The time to therapeutic level was defined as the time required from the first dose of vancomycin in a given modality to the first vancomycin steady state trough or $C_{ss}$ between 12-20mg/L. The total daily dose required for target concentration attainment was then calculated based on the patient’s dosing at this time.

Patients were then divided into four groups on a per course basis: those receiving CIV or IIV that attained target levels; and those receiving CIV or IIV who did not attain target levels. Patient age, sex, weight, baseline serum creatinine, and creatinine clearance were then compared between the groups using Fisher’s exact and Student’s t-test to determine if there were any demographic factors that influenced the patients’ ability to attain target levels based on dosing modality.

2.4.2.6 Number of vancomycin levels ordered

The number of vancomycin levels ordered was defined as the number of serum vancomycin peaks, troughs, or random levels ordered during a given course of vancomycin therapy. To account for differences in the duration of vancomycin therapy and the duration of the patients’ admissions, the number of vancomycin levels ordered was standardized to the number of dose adjustments per 7 days of inpatient vancomycin therapy.

2.4.2.7 Number of dose adjustments

The number of dose adjustments was defined as the number of times either the vancomycin dose or dose interval were changed on a given modality. Conversion from IIV to CIV was counted as an IIV dose adjustment. To account for differences in the duration of vancomycin therapy and the duration of the patients’ admission, the number of dose adjustments was standardized to the number of dose adjustments per 7 days of inpatient vancomycin therapy. Dose adjustments made within the first 24 hours of therapy were excluded because they represented instances of empiric dose adjustment in the absence of vancomycin steady state level results.
2.4.2.8 Duration of vancomycin therapy

The duration of vancomycin was calculated from the time of the first dose to the time of the last dose. The duration of vancomycin for patients receiving multiple courses for the same indication (e.g. PJI) was calculated by taking the sum of durations from all vancomycin courses.

2.4.2.9 Occurrence of other, non-nephrotoxic vancomycin adverse events

The number and types of adverse event attributed to vancomycin by either the attending medical team or Infectious Diseases consult service were recorded based on the dose modality the patient was receiving at the time of the adverse event.

2.4.2.9.1 Outpatient vancomycin patient safety

Patients discharged on vancomycin with follow-up at either SHSC or MGH were assessed for outpatient vancomycin safety. Nephrotoxic risk and renal injury were assessed by comparing the patient’s baseline serum creatinine at initiation of vancomycin therapy as an inpatient to the maximum serum creatinine value recorded as an outpatient.

2.4.2.10 Post-hoc 24 hour area under the curve analysis

After the analysis of the primary and secondary outcomes, we sought to investigate the relationship between 24 hour area under the curve (AUC$_{24h}$) and steady state trough or C$_{ss}$. All steady state serum vancomycin peaks and troughs or random levels were recorded for every vancomycin course. The AUC$_{24h}$ was then calculated for each level with relevant equations found in Appendix 5.4. We then identified all AUC$_{24h}$ that were determined by individualized pharmacokinetic calculations (i.e. AUC$_{24h}$ calculated by C$_{ss}$ with CIV or with a peak and trough for IIV). The steady state trough or C$_{ss}$ versus AUC$_{24h}$ was then graphed on a scatter plot using Microsoft Excel.

A classification and regression tree (CART) analysis (Salford Predictive Modeler® software suite, v8.2.0.782, San Diego, California) was then completed to determine an AUC$_{24h}$ breakpoint for nephrotoxic risk. Vancomycin courses were eligible for inclusion in the CART analysis if individualized pharmacokinetic calculated vancomycin AUC$_{24h}$ (i.e. AUC$_{24h}$ based on C$_{ss}$ for
CIV or based on steady state peak and trough for IIV) determined from vancomycin levels taken within 5 days of the highest serum creatinine were available.

2.5 Statistical analysis

2.5.1 Baseline patient characteristics and study outcomes

Continuous, nominal, and ordinal data for baseline patient characteristics and study outcomes were analyzed using GraphPad InStat (version 3.05, 32-bit for Win 95/NT; GraphPad Software Inc, La Jolla, California). Continuous data were expressed as mean ± standard deviation (SD) and analyzed using the two-tailed unpaired t-test with or without the Welch correction, for unequal or equal standard deviations, respectively. Nominal data were expressed as the proportion of the total number of patients and analyzed using Fischer’s exact test (odds ratio [OR], 95% confidence interval [95% CI], and p-value). Ordinal data were expressed as median and range and analyzed using the Mann-Whitney test. P-values <0.05 were considered statistically significant. Poisson regression was used to determine if there was a difference in the time to nephrotoxic risk between CIV and IIV and logrank test used to determine if there was a difference in nephrotoxic risk.

The group assignment of patients to IIV or CIV for demographic data was based on the final dosing regimen used for the patient. Demographic data (age, sex, hospital location, LOS at time of vancomycin initiation, indication for vancomycin, comorbidities including immunosuppression due to drugs, severity of illness on admission [APACHEII, Pitt Bacteremia score]) were only counted once to reflect the count based on the number of patients. Laboratory data were included for each course of vancomycin received.

Clinical and microbiological outcomes were assessed based on the results of the final related admission for the initial indication for vancomycin (survival, cure). The LOS at time of vancomycin initiation was based on the first course of vancomycin for a patient with 2 or more vancomycin courses. Total duration of vancomycin treatment was the sum of the number of days of treatment from each course of vancomycin and each admission for a given patient.
2.5.2 Identifying independent predictors of nephrotoxic risk and renal injury using a generalized estimating equation model

A generalized estimating equation (GEE) model [141] was used to determine if there were any potential factors that were predictive of nephrotoxic risk and renal injury. The GEE model was chosen because it is able to account for the correlation among observations on the same patient for those patients that received multiple courses of vancomycin.

Potential factors linked with nephrotoxicity from the literature [56, 60][9, 41, 42, 52-55, 59, 62, 67, 71, 99, 101] were included in the GEE: sex, age on admission, location of admission (ward versus ICU), hospital site (acute versus non-acute) length of stay at vancomycin initiation, CHF, DM, hematologic malignancy, bone marrow transplant, APACHE II score, Pitt bacteremia score, weight, dose modality at time of highest serum creatinine (CIV versus IIV), duration of vancomycin therapy at time of highest serum creatinine, highest vancomycin trough or $C_{ss}$ level, dose modality at time of highest vancomycin level, and concomitant use of diuretics, piperillin-tazobactam, aminoglycosides, NSAIDs, angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), radiocontrast, ciprofloxacin, PPIs, number of concomitant nephrotoxins, and number of concomitant agents known to cause acute interstitial nephritis (Appendix 5.2). Since the counts for patients at MGH and SHSC-SJR were too sparse to analyze, the hospital sites were divided into acute care (SHSC-BC and MGH) and non-acute care (SHSC-HC and SHSC-SJR).

An independent correlation structure for the GEE model was chosen. Bivariate analyses were completed to determine which variables were significantly associated with nephrotoxic risk ($p<0.05$). Variables identified as significantly associated with nephrotoxic risk were then assessed for multicollinearity using tolerance statistics, with a tolerance value $<0.4$ indicating the presence of multicollinearity. For instances in which multicollinearity was observed, only one member of a correlated set was retained for the final model.

The GEE model was built to determine the association of dose modality at time of highest sCr and nephrotoxic risk, controlling for other predictors of nephrotoxic risk and potential confounders. The one in ten rule was used to determine the number of predictors that could be included in the model [142]. To build the model, a stepwise, forward building approach was used. Firstly, the predictor of interest, dose modality at time of highest sCr, was included in the
model. Then the remaining variables were included in the model one by one in the order of decreasing effect size. If there was a change in the effect size $>10\%$ of the predictor of interest on outcome, then the variable was retained in the model [143]. Bivariate analyses, test for multicollinearity, and model building process were then repeated for renal injury. All analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC, USA).
Chapter 3

RESULTS
3 Results

3.1 Baseline patient characteristics

During the 7 year study period, a total of 2136 patients received $>48$ hours of vancomycin as an inpatient, and 146 (6.8%) patients across four study sites received continuous infusion vancomycin (CIV) (Figure 1). These patients were then matched to an equal number of patients who received intermittent infusion vancomycin (IIV). The baseline patient characteristics, indications, and microbiology can be seen in Table 2.
Figure 1: Schematic for patient allocation.
All patients had exact matches for sex and hospital location at time of vancomycin initiation. There were no significant differences between age (p=0.93) or length of stay at time of vancomycin initiation (p=0.60). Comorbid conditions were similar between both groups, but significantly fewer patients in the CIV cohort had congestive heart failure (CHF) compared to those receiving IIV (6 versus 16; odds ratio [OR] 0.35; 95% confidence interval [CI] 0.13-0.92; p=0.044). Critical illness was defined as an Acute Physiologic Assessment and Chronic Health Evaluation (APACHE II) score ≥20 [2] for patients in the ICU and Pitt bacteremia score ≥4 [140] for patients on the ward. There were no significant differences in the number of critically ill intensive care unit (ICU) and ward patients between the two cohorts.

The indications for vancomycin were similar between the two groups. However, more patients in the CIV group received vancomycin for a bone, joint, or hardware infection (65% vs 45%; OR 2.32; 95% CI 1.45-3.72, p=0.0006) and fewer received vancomycin for an intra-abdominal infection (1% vs 10%; OR 0.13; 95% CI 0.03-0.59; p=0.003).

The only significant microbiologic difference between the two groups was a lower incidence of infections caused by *E. faecium* in the CIV cohort compared to IIV (5 vs 17; OR 0.27; 95% CI 0.096-0.75; p=0.01). There were also fewer concomitant gram negative bacterial infections in patients receiving CIV than IIV, though this did not meet statistical significance (43 [29%) vs 59 [40%); OR 0.62, 95% CI 0.38-1.00; p=0.07).

**Table 2: Patient characteristics**

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>CIV (n=146)</th>
<th>IIV (n=146)</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male), no. (%)</td>
<td>89 (61%)</td>
<td>89 (61%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age on Admission (years), mean ± SD</td>
<td>57 ± 17</td>
<td>57 ± 19</td>
<td>-</td>
<td>-</td>
<td>0.93</td>
</tr>
<tr>
<td>Weight (kg), mean ± SD</td>
<td>87 ± 24</td>
<td>81 ± 27</td>
<td>-</td>
<td>-</td>
<td>0.05</td>
</tr>
<tr>
<td>Hospital Location at Vancomycin Initiation (ward), no. (%)</td>
<td>114 (78%)</td>
<td>114 (78%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Length of Stay at Initiation</td>
<td>9 ± 21</td>
<td>10 ± 18</td>
<td>-</td>
<td>-</td>
<td>0.60</td>
</tr>
<tr>
<td>Site of initiation, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHSC-BC</td>
<td>92 (63%)</td>
<td>127 (87%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHSC-HC</td>
<td>48 (33%)</td>
<td>17 (12%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MGH</td>
<td>6 (4%)</td>
<td>2 (1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Presence of comorbidities, no. (%) | | | |
|-----------------------------------|-----------------|-----------------|
| Congestive Heart Failure          | 6 (4%)          | 16 (11%)        |
| Chronic Obstructive Pulmonary Disease | 5 (3%)      | 7 (5%)          |
| Diabetes                         | 25 (17%)        | 34 (23%)        |
| Human immunodeficiency virus/Acquired Immune deficiency Syndrome | 0 (0%) | 0 (0%) |
| Asplenia                         | 2 (1%)          | 2 (1%)          |
| Hypogammaglobulinemia            | 0 (0%)          | 0 (0%)          |
| Haematologic Malignancy          | 4 (3%)          | 5 (3%)          |
| Bone Marrow Transplant           | 0 (0%)          | 1 (1%)          |
| Immunosuppressive Drug           | 16 (11%)        | 13 (9%)         |
| Any comorbidity or Immunosuppressive Drug use | 46 (32%) | 58 (40%) |

| Severity of illness | | | |
|---------------------|-----------------|-----------------|
| APACHE II, (ICU patients), median (range) | 18 (3-29) | 15 (0-30) |
| APACHE II > 20      | 10 (31%)        | 5 (15%)        |
| Pitt Bacteremia score (Ward patients), median [range] | 0 [0-4] | 0 [0-4] |
| Pitt Bacteremia score ≥ 4 | 2 (2%) | 3 (3%) |

| Indications, no. (%) | | | |
|----------------------|-----------------|-----------------|
| Primary Bacteremia   | 3 (2%)          | 5 (3%)          |
| Bone, Joint, and Hardware | 95 (65%) | 65 (45%) |
| Central nervous system | 14 (10%) | 15 (10%) |
| Central nervous system abscess | 4 (3%) | 14 (10%) |
| Genitourinary        | 0 (0%)          | 1 (1%)          |
| Cardiovascular       | 3 (2%)          | 8 (5%)          |
| Intra-abdominal      | 2 (1%)          | 14 (10%)        |
| Line-associated bacteremia | 3 (2%) | 5 (3%) |
| Lung                 | 2 (1%)          | 1 (1%)          |
| Skin and soft tissue | 19 (13%)        | 18 (12%)        |
| Unknown              | 1 (1%)          | 0 (0%)          |

| Microbiology, no. (%) | | | |
|-----------------------|-----------------|-----------------|
| CNST                  | 62 (42%)        | 63 (43%)        |
| MRSA                  | 24 (16%)        | 21 (14%)        |
| MSSA                  | 9 (6%)          | 9 (6%)          |
### Outcomes

#### Primary outcome

#### Nephrotoxicity

Per course serum creatinine (sCr) values can be seen in Table 3. Baseline sCr at the start of vancomycin therapy was similar between cohorts (p=0.63). However, following vancomycin initiation the average sCr peak in patients receiving IIV was higher than that seen in CIV (p=0.0036) and resulted in a larger average increase from baseline sCr in the IIV group (p=0.011).

<table>
<thead>
<tr>
<th></th>
<th>CIV</th>
<th>IIV</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial serum creatinine, mean ± SD</td>
<td>67 ± 22 (n=54)</td>
<td>69 ± 33 (n=293)</td>
<td>0.63</td>
</tr>
<tr>
<td>Final serum creatinine, mean ± SD</td>
<td>71 ± 33 (n=170)</td>
<td>77 ± 42 (n=177)</td>
<td>0.11</td>
</tr>
<tr>
<td>Highest serum creatinine up to 2 weeks after completing vancomycin, mean ± SD</td>
<td>79 ± 37 (n=129)</td>
<td>94 ± 53 (n=218)</td>
<td>0.0036</td>
</tr>
<tr>
<td>Greatest % change from baseline, mean ± SD</td>
<td>24.6% ± 52% (n=129)</td>
<td>40.6% ± 74.7% (n=218)</td>
<td>0.011</td>
</tr>
</tbody>
</table>
Fewer patients in the CIV cohort experienced nephrotoxic risk compared to the IIV cohort (12.4% vs 21.6%, OR 0.52, p=0.043), and IIV was associated with a four-fold higher risk of renal injury (3% vs 12%, OR 0.23, p=0.003) (Table 4). No CIV patients required renal replacement therapy (RRT), while two patients in the IIV cohort required RRT while receiving vancomycin therapy.

Table 4: Primary Outcome: nephrotoxic risk and renal injury

<table>
<thead>
<tr>
<th></th>
<th>CIV (N=129)</th>
<th>IIV (n=218)</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotoxic Risk</td>
<td>16 (12.4%)</td>
<td>47 (21.6%)</td>
<td>0.52</td>
<td>0.28-0.96</td>
<td>0.043</td>
</tr>
<tr>
<td>Renal Injury</td>
<td>4 (3.1%)</td>
<td>24 (12.4%)</td>
<td>0.23</td>
<td>0.077-0.66</td>
<td>0.003</td>
</tr>
<tr>
<td>Need for RRT</td>
<td>0 (0%)</td>
<td>2 (1%)</td>
<td>0.50</td>
<td>0.0098-4.32</td>
<td>0.21</td>
</tr>
</tbody>
</table>

3.2.1.2 Identification of independent predictors of nephrotoxic risk and renal injury using a generalized estimating equation model

A generalized estimating equation (GEE) was completed to account for the correlation among observations from the same patient. There was a total of 59 events that occurred for nephrotoxic risk and 28 events for renal injury. Therefore, based on the one in ten rule, a maximum of 6 and 3 variables were eligible for inclusion in the GEE models for nephrotoxic risk and renal injury, respectively [142].

The bivariate analyses identified the following variables as significantly associated with nephrotoxic risk: concomitant diuretic use, concomitant piperacillin-tazobactam use, dose modality at time of highest vancomycin concentration, serum creatinine at start of vancomycin, dose modality at time of highest serum creatinine, vancomycin duration at time of highest serum creatinine, and hospital site. A check for multicollinearity showed that dose modality at time of highest vancomycin level was found to be correlated with dose modality at time of highest sCr (tolerance <0.4) (Table 5). Therefore, only dose modality at time of highest sCr was retained in the multivariable GEE model.

Table 5: Check for multicollinearity for GEE model for nephrotoxic risk

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose modality at time of highest serum creatinine (CIV vs IIV)</td>
<td>0.38</td>
</tr>
<tr>
<td>Dose modality at time of highest sCr</td>
<td>0.39</td>
</tr>
</tbody>
</table>
vancomycin level (CIV vs IIV) | Vancomycin duration at time of highest serum creatinine | 0.94
| Concomitant nephrotoxin use | 0.73
| Concomitant diuretic use | 0.74
| Hospital site (non-acute versus acute) | 0.92
| Concomitant piperacillin-tazobactam use | 0.98

The GEE model was then built in a forward stepwise fashion. Variables were included in the final model if they caused a >10% change in the effect size for dose modality at time of highest sCr, and/or if they increased the precision in the effect size for dose modality at time of highest sCr (Table 6). Concomitant use of nephrotoxins and concomitant use of diuretic were excluded from the final model because they did not change the effect size by more than 10% or increase the precision for dose modality at the time of highest sCr. Although hospital site was not significant, it was retained in the final model because it caused a large change in the effect size. The model results showed that CIV was a negative predictor for nephrotoxic risk while controlling for concomitant piperacillin-tazobactam use, hospital site, and vancomycin duration at time of highest serum creatinine. Concomitant piperacillin-tazobactam use and vancomycin duration at time of highest serum creatinine were positive predictors.

**Table 6: GEE model results for nephrotoxic risk**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose modality at time of highest serum creatinine (CIV vs IIV)</td>
<td>0.46</td>
<td>0.24-0.91</td>
<td>0.025</td>
</tr>
<tr>
<td>Concomitant piperacillin-tazobactam use</td>
<td>3.58</td>
<td>1.70-7.54</td>
<td>0.001</td>
</tr>
<tr>
<td>Hospital site (non-acute vs acute)</td>
<td>0.48</td>
<td>0.21-1.10</td>
<td>0.084</td>
</tr>
<tr>
<td>Vancomycin duration at time of highest sCr</td>
<td>1.04</td>
<td>1.02-1.05</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Bivariate analyses identified the following variables as significantly associated with renal injury: dose modality at time of highest sCr, concomitant piperacillin-tazobactam use, sCr at start of vancomycin therapy, and vancomycin duration at time of highest sCr. The check for
multicollinearity did not identify any variable as significantly associated with one another (Table 7).

**Table 7: Check for multicollinearity for GEE model for renal injury**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose modality at time of highest serum creatinine (CIV vs IIV)</td>
<td>0.97</td>
</tr>
<tr>
<td>Vancomycin duration at time of highest serum creatinine</td>
<td>0.97</td>
</tr>
<tr>
<td>Serum creatinine at vancomycin initiation</td>
<td>0.98</td>
</tr>
<tr>
<td>Concomitant piperacillin-tazobactam use</td>
<td>0.99</td>
</tr>
</tbody>
</table>

The GEE model to predict renal injury was built in a forward, stepwise fashion as described for nephrotoxic risk. Concomitant piperacillin-tazobactam use and sCr at the start of vancomycin therapy were excluded from the final model because they caused a <10% change in the effect size of dose modality at time of highest serum creatinine. CIV was found to be a significant negative predictor of renal injury and vancomycin duration at time of highest serum creatinine was a significant positive predictor (Table 8).

**Table 8: GEE model results for renal injury**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose modality at time of highest serum creatinine (CIV vs IIV)</td>
<td>0.19</td>
<td>0.05-0.59</td>
<td>0.004</td>
</tr>
<tr>
<td>Vancomycin duration at time of highest sCr</td>
<td>1.03</td>
<td>1.01-1.05</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

The time to nephrotoxic risk can be seen in Figure 2. The logrank test identified a significant difference in the incidence of nephrotoxic risk between CIV and IIV (p=0.0012), but Poisson regression did not identify a significant difference in the time to nephrotoxicity (p=0.63). Days of therapy until time of highest sCr was associated with nephrotoxic risk in the IIV cohort (p<0.001) but not the CIV cohort (p=0.26).
*Note: CIV duration was truncated from 169 days to 83 days to permit analysis of differences between the two cohorts.

**Figure 2: Time to nephrotoxic risk.**

### 3.2.2 Secondary Outcomes

#### 3.2.2.1 Clinical outcomes, microbiologic outcomes, survival, and attributable mortality

62 patients in the CIV cohort and 67 patients in the IIV cohort met the criteria to be eligible for assessment of clinical cure; and 40 patients in the CIV cohort and 39 patients in the IIV cohort were eligible for assessment of microbiologic cure. There were no significant differences in clinical cure, microbiologic cure, survival and attributable mortality between the CIV and IIV cohorts (Table 9).

**Table 9: Clinical cure, microbiologic cure, survival and attributable mortality**

<table>
<thead>
<tr>
<th></th>
<th>CIV</th>
<th>IIV</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Cure, no. (%)</td>
<td>62/67 (93%)</td>
<td>58/62 (94%)</td>
<td>1.17</td>
<td>0.30-4.57</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Microbiologic Cure, no. (%)</td>
<td>37/40 (93%)</td>
<td>33/39 (85%)</td>
<td>0.45</td>
<td>0.10-1.93</td>
<td>0.31</td>
</tr>
<tr>
<td>Survival*, no. (%)</td>
<td>138/141 (98%)</td>
<td>135/142 (95%)</td>
<td>2.38</td>
<td>0.60-9.41</td>
<td>0.33</td>
</tr>
<tr>
<td>Attributable mortality*, no. (%)</td>
<td>2/141 (1%)</td>
<td>4/142 (3%)</td>
<td>0.50</td>
<td>0.09-2.75</td>
<td>0.69</td>
</tr>
</tbody>
</table>
**: 9 patients (5 CIV and 4 IIV) were excluded from survival analysis because they were transferred to another facility with no follow up.

### 3.2.2.2  Initial and final vancomycin total daily doses and corresponding vancomycin levels

The initial vancomycin level for patients receiving CIV was 12.78mg/L, which was significantly higher than the initial level of 9.87mg/L in patients receiving IIV (p=0.0001). Although the CIV C\textsubscript{ss} was higher than the IIV steady state trough concentration, the average daily dose that corresponded to these levels was significantly lower with CIV vs IIV (CIV: 2047mg ± 466mg [range: 1000-3750mg] vs IIV: 2195mg ± 626mg [range: 500-4500mg]; p=0.03). It is important to note that these average doses would be rounded to 2000 mg and 2250mg for CIV and IIV real life administration, respectively. The final average vancomycin level for patients receiving CIV was 16.24mg/L compared to a final average steady state trough concentration of 14.43mg/L (p=0.0007) for patients receiving IIV. The mean total daily vancomycin dose required to achieve the final levels were 2098mg ± 766mg (range: 600-4000mg) and 2195mg ± 1029mg (range: 500-8000mg) for CIV and IIV, respectively (p=0.32); which would be rounded to 2000mg and 2250 mg for dosing administration in practice, respectively.

#### Table 10: Initial and final total daily vancomycin doses and corresponding steady state random level or trough.

<table>
<thead>
<tr>
<th></th>
<th>CIV</th>
<th>IIV</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial total daily dose (mg), mean ± SD, [range]</td>
<td>2047 ± 466 [1000-3750] (n=74)</td>
<td>2195 ± 626 [500-4500] (n=273)</td>
<td>0.027</td>
</tr>
<tr>
<td>Initial level (mg/L), mean ± SD, [range]</td>
<td>12.78 ± 5.40 [1.99-27.49] (n=74)</td>
<td>9.87 ± 5.73 [1.99-32.14] (n=273)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Final total daily dose (mg), mean ± SD, [range]</td>
<td>2098 ± 766 [600-4000] (n=162)</td>
<td>2195 ± 1029 [500-8000] (n=185)</td>
<td>0.32</td>
</tr>
<tr>
<td>Final level (mg/L), mean ± SD, [range]</td>
<td>16.24 ± 2.91 [6.54-46.16] (n=162)</td>
<td>14.43 ± 5.40 [2.91-29.28] (n=185)</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

#### 3.2.2.3  Attainment of target levels 12-20mg/L

Diagram of assessment of attaining target level based on dose modality can be seen below in Figure 3 and results for attaining target levels can be seen in Table 11. A greater proportion of patients receiving CIV (103/127 [81%]) were able to achieve target levels of 12-20mg/L.
compared to patients receiving IIV (176/293 [60%]; OR 2.85, 95% CI 1.73-4.71, p<0.0001).
Those receiving CIV were also able to obtain target levels in less time than those receiving IIV (2.27 days vs 5.17 days; p<0.0001), but had similar necessary mean doses (2386mg vs 2567, p=0.079) to achieve target.

Figure 3: Patient flow and assessment of target vancomycin levels.
Table 11: Characteristics for attainment of target levels 12-20mg/L

<table>
<thead>
<tr>
<th></th>
<th>CIV (n=127)</th>
<th>IIV (n=293)</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attainment of target level 12-20mg/L, no. (%)</td>
<td>103/131 (79%)</td>
<td>176/293 (60%)</td>
<td>2.44</td>
<td>1.52-3.95</td>
<td>0.0002</td>
</tr>
<tr>
<td>Days to achieve C&lt;sub&gt;ss&lt;/sub&gt; or trough of 12-20mg/L, mean ± SD, [range]</td>
<td>2.27 ± 1.77 [0.03-12.90]</td>
<td>5.17 ± 4.64 [0.03-22.23]</td>
<td>-</td>
<td>-</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dose required, mean ± SD, [range]</td>
<td>2386 ± 739 [750-4500]</td>
<td>2567 ± 965 [500-6000]</td>
<td>-</td>
<td>-</td>
<td>0.079</td>
</tr>
</tbody>
</table>

We completed an additional analysis of patient demographics that may have affected patients’ ability to achieve therapeutic levels (Table 12). Patients receiving CIV who attained target vancomycin concentrations were younger, weighed more, and had a greater creatinine clearance than IIV patients who attained target levels.

Table 12: Comparison of patient demographics for CIV and IIV courses that achieved target concentrations.

<table>
<thead>
<tr>
<th></th>
<th>CIV (n=103)</th>
<th>IIV (n=176)</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Male), no. (%)</td>
<td>62 (60.2%)</td>
<td>103 (58.5%)</td>
<td>1.07</td>
<td>0.65-1.76</td>
<td>0.80</td>
</tr>
<tr>
<td>Age on Admission (Years), mean ± SD</td>
<td>56.3 ± 18.5</td>
<td>60.4 ± 18.0</td>
<td>-</td>
<td>-</td>
<td>0.075</td>
</tr>
<tr>
<td>Hospital Location at Vancomycin Initiation (Ward), no. (%)</td>
<td>81 (78.6%)</td>
<td>138 (78.4%)</td>
<td>1.01</td>
<td>0.56-1.83</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Weight (kg), mean ± SD</td>
<td>89.2 ± 24.6</td>
<td>79.2 ± 22.0</td>
<td>-</td>
<td>-</td>
<td>0.0005</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L), mean ± SD</td>
<td>66.0 ± 25.1</td>
<td>71.0 ± 33.3</td>
<td>-</td>
<td>-</td>
<td>0.19</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min), mean ± SD</td>
<td>130.0 ± 65.6</td>
<td>110.6 ± 66.1</td>
<td>-</td>
<td>-</td>
<td>0.018</td>
</tr>
</tbody>
</table>

The results were similar when we compared patients receiving IIV who did not attain target vancomycin concentrations versus IIV patients who attained target concentrations. Patients receiving IIV who did not attain target levels were younger, weighed more and had a greater creatinine clearance than patients who attained target concentration (Table 13).
Table 13: Comparison of patient demographics for IIV patients who did and did not achieve target vancomycin concentrations.

<table>
<thead>
<tr>
<th></th>
<th>IIV not therapeutic (n=40)</th>
<th>IIV therapeutic (n=176)</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Male), no. (%)</td>
<td>30 (75.0%)</td>
<td>103 (58.5%)</td>
<td>1.30</td>
<td>0.53-3.16</td>
<td>0.071</td>
</tr>
<tr>
<td>Age on Admission (Years), mean ± SD</td>
<td>49.1 ± 17.3</td>
<td>60.4 ± 18.0</td>
<td>-</td>
<td>-</td>
<td>0.0004</td>
</tr>
<tr>
<td>Hospital Location at Vancomycin Initiation (Ward)</td>
<td>33 (82.5%)</td>
<td>138 (78.4%)</td>
<td>2.13</td>
<td>0.98-4.62</td>
<td>0.67</td>
</tr>
<tr>
<td>Weight (kg), mean ± SD</td>
<td>90.9 ± 30.8</td>
<td>79.2 ± 22.0</td>
<td>-</td>
<td>-</td>
<td>0.0054</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L), mean ± SD</td>
<td>68.1 ± 37.0</td>
<td>71.0 ± 33.3</td>
<td>-</td>
<td>-</td>
<td>0.62</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min), mean ± SD</td>
<td>138.8 ± 60.3</td>
<td>110.6 ± 66.1</td>
<td>-</td>
<td>-</td>
<td>0.014</td>
</tr>
</tbody>
</table>

3.2.2.4 Number of vancomycin levels ordered and dose adjustments completed

When standardized to 7 days of vancomycin therapy, CIV patients had significantly fewer vancomycin levels drawn and required fewer dosing adjustments (Table 14).

Table 14: Mean number of vancomycin levels ordered and dose adjustments per 7 days of therapy.

<table>
<thead>
<tr>
<th></th>
<th>CIV</th>
<th>IIV</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of vancomycin levels per 7 days, mean ± SD</td>
<td>2.94 ± 1.63</td>
<td>3.38 ± 2.28</td>
<td>0.017</td>
</tr>
<tr>
<td>Number of times vancomycin dose adjusted per 7 days, mean ± SD</td>
<td>0.68 ± 0.91</td>
<td>1.53 ± 1.66</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

3.2.2.5 Theoretical IIV dose required to achieve therapeutic levels

We identified 88 patients who were initially on IIV and later converted to CIV. As per section 3.2.2.3, patients receiving IIV who did not attain target levels tended to be younger, had a higher weight and greater creatinine clearance than their counterparts who were able to attain target levels while receiving IIV. Patients who were initially on IIV and later converted to CIV had a mean initial steady state trough concentration of 11.86 ± 5.23mg/L with an initial total daily dose of 2368 ± 6.58mg on IIV vancomycin. If these patients had continued on IIV vancomycin, in
order to achieve a final steady state trough of 15mg/L they would have required an average total daily IIV dose of 5280mg/L. In contrast, they were able to attain a target Css with CIV dosing at a mean actual final total daily dose of 2162mg/L (p<0.0001) (Table 15).

Table 15: Theoretical IIV dose versus actual CIV dose required to achieve trough of 15mg/L.

<table>
<thead>
<tr>
<th></th>
<th>CIV (n=88)</th>
<th>IIV (n=88)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicted total daily dose to achieve steady state level 15mg/L, (mg) mean ± SD</td>
<td>2162 ± 863</td>
<td>5280 ± 3436</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

3.2.2.6 Duration of vancomycin therapy

The mean total duration of vancomycin was 39 ± 24 days for those receiving IIV compared to 46 ± 31 days in patients receiving CIV (p=0.05).

3.2.2.7 Occurrence of other, non-nephrotoxic vancomycin-associated adverse events

The total number of other vancomycin-associated adverse events can be seen in Table 16. The most common adverse event was rash, which occurred more frequently when patients received CIV compared to IIV, though it did not meet statistical significance (OR 4.32; 95% CI 0.90-20.66; p=0.057). There were no significant differences in the incidences for the remaining adverse events, with an occurrence rate of 0-2%. All adverse events led to the discontinuation of vancomycin therapy.

Table 16: Other vancomycin-associated adverse events that led to treatment discontinuation

<table>
<thead>
<tr>
<th></th>
<th>CIV (N=170)</th>
<th>IIV (n=177)</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of adverse drug reactions</td>
<td>12 (7%)</td>
<td>8 (5%)</td>
<td>1.58</td>
<td>0.63 – 3.98</td>
<td>0.36</td>
</tr>
<tr>
<td>Rash</td>
<td>8 (5%)</td>
<td>2 (1%)</td>
<td>4.32</td>
<td>0.90 - 20.66</td>
<td>0.057</td>
</tr>
<tr>
<td>Redman syndrome</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>3.14</td>
<td>0.13 - 77.72</td>
<td>0.49</td>
</tr>
<tr>
<td>Fever</td>
<td>3 (2%)</td>
<td>0 (0%)</td>
<td>7.42</td>
<td>0.38 - 144.80</td>
<td>0.12</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0 (0%)</td>
<td>2 (1%)</td>
<td>0.21</td>
<td>0.0098 - 4.32</td>
<td>0.50</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>0.34</td>
<td>0.014 - 8.54</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>3.14</td>
<td>0.13 - 77.72</td>
<td>0.49</td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>3.14</td>
<td>0.13 - 77.72</td>
<td>0.49</td>
</tr>
</tbody>
</table>
3.2.2.8 Outpatient safety

There were a limited number of outpatient files available for review. A total of 252 outpatient charts were requested, 59 (23%) were available and these were reviewed. Two patients who had previously completed a course of CIV were restarted by a SHSC infectious diseases physician as an outpatient. There were a total of 41 files for CIV patients and 18 files for IIV patients who received outpatient therapy (Table 17). Zero patients in the CIV cohort experienced nephrotoxic risk compared to 3 (17%) in the IIV cohort (OR 0.05, 95% CI 0.0026-1.094; p=0.025); and only 1 (6%) IIV patient experienced renal injury (OR 0.14, 95% CI 0.0055-3.62; p=0.31).

Table 17: Safety outcomes for patients receiving outpatient vancomycin therapy

<table>
<thead>
<tr>
<th></th>
<th>CIV (N=41)</th>
<th>IIV (n=18)</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotoxic Risk</td>
<td>0 (0%)</td>
<td>3 (17%)</td>
<td>0.053</td>
<td>0.0026 - 1.09</td>
<td>0.025</td>
</tr>
<tr>
<td>Renal Injury</td>
<td>0</td>
<td>1 (6%)</td>
<td>0.14</td>
<td>0.0055 - 3.62</td>
<td>0.31</td>
</tr>
</tbody>
</table>

3.2.2.9 Assessment of 24 hour area under the curve

As a post-hoc exploratory analysis, we calculated the AUC$_{24h}$ for every vancomycin level drawn (Appendix 5.4). AUC$_{24h}$ calculated with individualized pharmacokinetics (i.e. patients receiving CIV or patients receiving IIV who had a peak and trough drawn) were then plotted on a scatter plot versus the trough or random level (Figure 4). From the figure, it is apparent that patients on IIV may have had an AUC$_{24h}$$\geq$400 with a vancomycin trough concentration of <15mg/L.
A total of 271 courses of vancomycin were eligible for CART analysis. We identified an $AUC_{24h}$ breakpoint of 515 for nephrotoxic risk (Figure 5). The resulting specificity was 94%, and sensitivity was 13%. CART analysis was repeated with vancomycin steady state random concentrations and troughs. We found the nephrotoxic risk occurred in <5% of those with a $C_{ss}$ or trough <15mg/L and 20% when the $C_{ss}$ or trough was >15mg/L, in keeping with published literature [14].

Figure 4: Relationship between calculated 24 hour area under the curve versus steady state vancomycin trough or random concentration.
Sample Size: 271

Nephrotoxic Risk
Yes: 39
No: 232

AUC ≤ 515 mg*h/L
Nephrotoxic Risk
Yes: 34 (13.5%)
No: 218 (86.5%)

AUC > 515 mg*h/L
Nephrotoxic Risk
Yes: 5 (35.7%)
No: 14 (64.3%)

Figure 5: CART analysis results for 24 hour area under the curve and nephrotoxic risk.
Chapter 4

DISCUSSION AND CONCLUSION
4 Discussion and Conclusion

Previous studies comparing the two dose modalities concluded comparable efficacy between continuous infusion vancomycin (CIV) and intermittent infusion vancomycin (IIV). [96, 97, 105, 111, 121] We did not think we would have the sample size to identify a significant difference in clinical outcome between the two dose modalities. Since the reported benefit of CIV over IIV is a decreased risk in nephrotoxicity, we chose vancomycin associated nephrotoxicity (VAN) as the primary outcome for our study. This would allow us to include patients with concomitant or culture-negative infections in the study, something we would not have been able to do if efficacy was a co-primary outcome.

4.1 Patient demographics

The patients were well matched at baseline for age, sex, hospital location when initiating vancomycin, and length of stay at time of vancomycin initiation. There were two risk factors for VAN that were different between the two modalities: more patients in the IIV cohort had congestive heart failure (CHF) while patients in the CIV cohort had a greater baseline weight. However, both factors were not found to be predictors of nephrotoxicity using the generalized estimating equation (GEE) bivariate analyses.

The indications were mostly balanced between the two cohorts. However, more patients in the CIV cohort received vancomycin for bone, joint and hardware infections while more patients in the IIV cohort received vancomycin for intra-abdominal infections. These differences are in keeping with the practices at our site: indications requiring prolonged courses of vancomycin, such as prosthetic joint infections, were either started on CIV or converted to CIV, while IIV was used for indications that have shorter durations of therapy, like intra-abdominal infections. There were also more patients in the IIV cohort who received vancomycin for a central nervous system (CNS) abscess compared to those in the CIV cohort, which was not expected since CIV would be the preferred modality for longer duration indications. Further investigation identified a range of reasons why this was the case: 1 patient was repatriated to a different hospital; 1 patient passed away; 3 patients discontinued vancomycin due to adverse events; and 5 were treated in 2011 before CIV was implemented. There were more IIV patients treated for infections where
the isolated pathogen was *E. faecium*, which was the result of the increased number of intra-abdominal infection (IAI) in the IIV cohort.

4.2 Vancomycin associated nephrotoxicity in CIV and IIV patients

In this retrospective, multicentre matched cohort study, patients receiving CIV were less likely to experience nephrotoxic risk (OR 0.46, 95% CI 0.24-0.91, p=0.025) and renal injury (OR 0.19, 95% CI 0.05-0.59, p=0.004), as defined by the RIFLE criteria.

The reported risk of vancomycin associated nephrotoxicity ranges from 0-40% [8, 40] based on differences in patient populations and study designs, but is commonly cited at approximately 20%. [48] Earlier studies used varying definitions of nephrotoxicity, but more recent studies have been adopting more consistent definitions, including the RIFLE criteria [1] or Acute Kidney Injury Network (AKIN) classification [144]. We chose to use the nephrotoxic risk and renal injury definitions of the RIFLE criteria for our study because AKIN requires at least two serum creatinine values within 48 hours to define an acute kidney injury. [144] Therefore, we would have missed identifying an acute kidney injury (AKI) in the more stable patients who had blood work done once or twice weekly.

Patients who received CIV were less likely to develop increases in serum creatinine (sCr) resulting in nephrotoxic risk compared to those who received IIV (12.4% vs 21.6%; OR 0.52; 95% CI 0.28-0.96; p=0.043). The rate of nephrotoxicity in this study among the IIV cohort (21.6%) was similar to the 20% most frequently cited in the literature. Those receiving CIV had an OR of 0.52 of developing VAN compared to the IIV cohort. After adjusting for the imbalances and differences between the two cohorts with the GEE, CIV remained an independent predictor of decreased nephrotoxic risk (Table 6) and renal injury (Table 8). Although the risk of nephrotoxicity was increased with duration of therapy, CIV had a reduced risk of nephrotoxicity at all time points was seen with CIV versus IIV based on time to event analyses.

Two patients receiving IIV would eventually go on to require renal replacement therapy (RRT). However, it should be noted that both patients would eventually pass secondary to the infection for which vancomycin was indicated. Therefore, it was uncertain if dialysis was indicated for vancomycin associated nephrotoxicity or multi-organ failure secondary to uncontrolled infection.
4.3 Incidence of other vancomycin-associated adverse events

The rates of other adverse events, including ototoxicity, fever, and hematologic derangements were low (<1-2%) and comparable between modalities. Numerically, there were more courses of CIV that caused rash than IIV (8 [5%] vs 2 [1%]; OR 4.32, 95% CI 0.90-20.66; p=0.057). However, the rashes occurred over a 6 year study time span and the incidence observed in this study with CIV is comparable to the literature reported rates of rash with vancomycin IIV of 6%. [145]

4.4 Secondary outcomes: clinical cure, microbiological cure, and attributable mortality

There were no statistically significant differences in clinical cure, microbiological cure, and attributable mortality between CIV and IIV.

Only subsets of patients were included in the assessment for clinical cure given the strict study criteria. The study rate of clinical cure with vancomycin was approximately 90% and is higher than literature reported rates of 60-80%. [36, 41, 71, 146, 147] However, it should be noted that most studies that have looked at the efficacy of vancomycin, have assessed cure for methicillin resistant *Staphylococcus aureus* (MRSA) infections in the intensive care unit (ICU). This study had a relatively low incidence of MRSA infections (14-16%) and less pathogenic Gram-positive bacteria were more commonly seen. The high survival rate among the CIV and IIV cohorts (98% and 95%, respectively) may also be a reflection of the types of infections seen in this study. Two-thirds of the indications were bone, joint and hardware infections and non-severe skin and soft tissue infections; both of which have lower 14 day mortality rates compared to pneumonia or infective endocarditis. [148]

4.5 Vancomycin doses and achievement of therapeutic levels

Ingram et al. [100] identified a 21-fold increase in nephrotoxicity when $C_{ss} \geq 28$mg/L, and showed a risk of approximately 20% at a $C_{ss}=20$mg/L. Since a risk of up to 20% is considered tolerable with IIV targeting troughs up to 20mg/L [36, 41, 71, 146, 147], we chose a $C_{ss}$ target of 12-20mg/L rather than the 20-25mg/L target originally chosen by Wysocki et al. [97] First, there is no evidence of increasing vancomycin minimum inhibitory concentrations (MICs) in Canadian strains of MRSA. [149] Therefore, a $C_{ss}$ of 16.7mg/L would be adequate to achieve the 24 hour
area under the curve (AUC$_{24h}$):MIC target ratio of 400. Secondly, since there is data supporting the attainment of an AUC$_{24h}$≥400mg*h/L with trough concentrations <15mg/L, a trough range between 12-20mg/L may be clinically appropriate from both an efficacy and safety perspective and matches the recommended target range of IIV for complicated MRSA infections in the literature. [37, 93]. Finally, the guideline target AUC$_{24h}$:MIC≥400 was identified in patients with MRSA pneumonia, and then extrapolated to other infections. [14, 37] There is still uncertainty on the optimal AUC$_{24h}$:MIC target for efficacy in other infections, like coagulase negative Staphylococci (CNST) prosthetic joint infections (PJI), which was the most common pathogen and indication in this study. Many of the clinicians at the study sites routinely recommended troughs or C$_{ss}$ of 12-20mg/L for CNST PJI based on their clinical experience.

Patients in the CIV cohort were able to achieve target vancomycin levels in 2.27 days compared to 5.17 days in the IIV cohort. In the future, it would be worthwhile to assess whether achieving therapeutic levels faster would lead to improved clinical outcomes; unfortunately our study design precluded this assessment.

The initial vancomycin dose was significantly lower in the CIV cohort compared to the IIV cohort (2047mg vs 2195mg, $p=0.027$), which would translate to a clinically used average dose of 2000mg vs 2250mg in the CIV vs IIV cohorts, respectively. The CIV cohort achieved higher initial steady state vancomycin levels compared to those receiving IIV (12.78mg vs 9.87mg, $p=0.0001$) at lower total daily initial doses.

Initially, we hypothesized patients receiving CIV would require lower total daily doses to achieve similar serum vancomycin levels compared to IIV. Our initial observations did not support this, since we found that the initial and final total daily doses for the CIV cohort were comparable to the IIV cohort. However, when the demographics for patients that attained target levels while receiving CIV versus those that attained target levels while receiving IIV were compared, we found the CIV patients were younger (56.3 years vs 60.4 years, $p=0.074$), weighed more (89.2kg vs 79.2kg, $p=0.0005$), and had better renal function (CrCl of 130.0mL/min vs 110.6mL/min, $p=0.018$). Similar observations were seen when we compared those who received IIV and did not achieve target levels to those who received IIV and did achieve target levels; those who did not attain target levels were younger (49.1 years vs 60.4 years, $p=0.0004$),
weighed more (90.9kg vs 79.2kg, p=0.0054), and had better renal function (CrCl of 138.8mL/min vs 110.6mL/min, p=0.014).

Therefore, older patients, who weighed less and had a decreased renal function were more likely to attain target level while receiving IIV. Conversely, younger patients, patients with higher creatinine clearance (i.e. those able to clear vancomycin) and patients who weighed more (i.e. had a larger volume of distribution) were less likely to attain target levels with safe doses of IIV. Although all patients may benefit from receiving CIV, patients who are younger, weigh more, and have better renal function would benefit the most from having their vancomycin modality changed from IIV to CIV.

Another possible explanation for the lack of any difference in the average dosing required to achieve target concentrations between IIV and CIV modalities was that patients who were initially on IIV and would have required unacceptably high doses of IIV to achieve target levels were converted to CIV. To determine if this was true we identified patients initially on IIV and converted to CIV, and we compared the final CIV dose used to attain target levels with the predicted IIV dose that would have been required for a trough of 15mg/L. We found that the predicted IIV dose was significantly higher than the final CIV dose the patient received (5280mg vs 2162mg, p<0.0001).

4.6 Therapeutic drug monitoring and dose adjustments

The CIV cohort had fewer vancomycin levels ordered and required fewer dose adjustments compared to the IIV cohort. This observation translates to improved convenience for the patient and health care providers (nursing, laboratory personnel, pharmacy technicians, pharmacists, and physicians), and reduced costs (reduced vancomycin dose, and decreased health care personnel time related to vancomycin related care issues).

4.7 Post hoc analysis

Despite having similar doses between the two dose modalities, the results of the study still identified CIV as independently protective against VAN. We hypothesized the risk of VAN is lower in CIV than IIV because CIV would have a decreased $\text{AUC}_{24h}$. We gathered data for every patient’s steady state serum peak, trough, and $C_{ss}$ vancomycin level to calculate $\text{AUC}_{24h}$ (Appendix 5.4). A total of 936 $\text{AUC}_{24h}$ were calculated: 290 for patients receiving IIV and 646
for patients receiving CIV. We then generated a scatter plot of the steady state serum vancomycin trough or $C_{ss}$ level versus $AUC_{24h}$.

When visually inspecting the scatter plot, there are several notable features. First: there is a linear relationship between $C_{ss}$ and $AUC_{24h}$, since $AUC_{24h}$ is a calculation incorporating $C_{ss}$. Second, almost every IIV steady state trough produced a greater $AUC_{24h}$ compared to an equal CIV $C_{ss}$. For example, a CIV $C_{ss}$ of 15mg/L produced an $AUC_{24h}$ of 360mg*h/L, but an IIV steady state trough of 15mg/L produced $AUC_{24h}$ ranging from 385-688mg*h/L. If higher $AUC_{24h}$ are correlated with VAN, then the range of $AUC_{24h}$ for a given trough may explain why patients with troughs of 15-20mg/L experience an increased risk of nephrotoxicity.

Thirdly, an average trough of 11.00mg/L and 15.95mg/L were required to attain an $AUC_{24h}$ of 350-400 and 400-699mg*h/L, respectively. This also demonstrated the guideline’s target trough recommendation of 15-20mg/L as a surrogate for $AUC_{24h} \geq 400$mg*h/L as reasonable. However, of the pharmacokinetic calculated $AUC_{24h}$ that were $\geq 400$mg*h/L for patients receiving IIV, we found that 58 (41%) had a troughs <15mg/L and 8 (6%) had a troughs <10mg/L. Furthermore, steady state troughs as low as 6.21 and 6.44mg/L were able to attain an $AUC_{24h} \geq 350$ and $\geq 400$mg*h/L, respectively. A previous study found that 68% of the $AUC_{24h}$ that were $\geq 400$mg*h/L had a trough <15mg/L and 31% <10mg/L, but included younger patients (average 47-50 years) with greater creatinine clearances (127-147mL/min) who would therefore be more likely to have lower troughs. [95] Thus, if clinicians increase the patient’s vancomycin dose in response to troughs <15mg/L, they may be increasing the $AUC_{24h}$ to potentially nephrotoxic levels.

We then sought to establish a relationship between $AUC_{24h}$ and nephrotoxic risk. While we were able to complete classification and regression tree analysis (CART) analysis to try to determine the $AUC_{24h}$ breakpoint for nephrotoxicity, the results were disappointing: the $AUC_{24h}$ breakpoint of 515mg*h/L had a sensitivity of 13% and specificity of 94%. The main limitation of the CART analysis was the large number of exclusions because individuals did not have a pharmacokinetic-calculated $AUC_{24h}$ at the time of their highest serum creatinine. The $AUC_{24h}$ we identified was lower than the threshold of 563 proposed by Chavada et al. [51] and 600-800 range proposed by
Given the limitations of this study and the published data [51, 66], more rigorous exploration of the AUC\textsubscript{24h} threshold for VAN is warranted.

### 4.8 Implications of Findings

We found that patients receiving CIV had a lower nephrotoxic risk and lower occurrence of renal injury compared to IIV with no change in clinical outcomes. After including potential confounders in the GEE model, CIV was found to be a negative predictor for both nephrotoxic risk and renal injury, when controlling for concomitant piperacillin-tazobactam use, hospital site, and vancomycin duration at the time of highest sCr. Therefore, CIV can be used as an alternative dosing strategy to minimize the risk of nephrotoxicity in those at increased risk of nephrotoxicity (e.g. prolonged duration over 14 days and IIV calculated daily doses ≥ 4g).

Only older patients, those with reduced renal function, and those of lower weight were able to attain therapeutic vancomycin trough concentrations with IIV; explaining the lack of difference in required total daily dose for those patients that acquired therapeutic concentrations in the IIV versus CIV cohorts. Patients who were unable to achieve therapeutic concentrations with IIV were switched to CIV and would have needed significantly higher vancomycin doses if they had been continued on IIV.

The ideal monitoring parameters for minimizing VAN still remains unknown. Although the guideline recommended steady state trough target of 15-20mg/L were able to generate AUC\textsubscript{24h}>400mg*h/L, we do not know what the AUC\textsubscript{24h} values are associated with VAN. More recent studies have suggested an AUC\textsubscript{24h} of 563-800mg*h/L as a conservative upper limit. [51, 66, 93] Additionally, since troughs <15mg/L were able to generate therapeutic AUC\textsubscript{24h}, this raises the question of whether clinicians should also be routinely recommending serum vancomycin peaks to accurately calculate individualized pharmacokinetics to determine AUC\textsubscript{24h} versus the use of the commonly used Rodvold population based nomogram. [4]

### 4.9 Strengths

The SPIRIT database provided a large number of potential patients to be included in the study. Furthermore, the large number of patients receiving IIV allowed us to match many of the patients’ baseline demographics, minimizing the number of potential confounders. We had a large sample size and were able to identify a statistically significant difference in our primary
outcome between the two cohorts. Although there were statistically significant differences identified between the baseline characteristics for the two cohorts, the GEE model did not identify any of them as significantly associated with nephrotoxic risk. The final GEE model still identified CIV as a negative predictor for both nephrotoxic risk and renal injury, when controlling for other predictors and potential confounders.

We were also able to collect a large amount of pharmacokinetic data for vancomycin since the primary study site recommends drawing vancomycin peaks and troughs for all patients in whom a trough vancomycin concentration between 15-20mg/L is targeted. This allowed us to calculate almost 1000 AUC\textsubscript{24h} and explore the relationship between steady state vancomycin trough and or C\textsubscript{ss}, AUC\textsubscript{24}, and VAN.

4.10 Weaknesses

The retrospective nature of the study was the major limitation of the study. First, the target trough or C\textsubscript{ss} level was not documented in the patient’s chart or EPR for every patient. Second, peaks and troughs were assumed to have been taken 2 hours after completion of the vancomycin infusion and just prior to the next dose, respectively. Lastly, the ordering of vancomycin levels was left to the discretion of the attending team who did not always follow the institutional guidelines.

There were 252 patients that were eligible to be assessed for VAN as an outpatient, but only 59 (23.4%) patient charts were found and reviewed. However, it was promising that we were able to identify CIV as having a significantly lower risk of VAN with the limited outpatient sample size, further investigation is warranted.

The heterogenous study population can be seen as both a strength and weakness. While most published studies focus on one type of infection caused by one pathogen (e.g. lower respiratory tract infections with \textit{S. aureus}), we accepted all infections and all pathogens which may improve the generalizability of our study. We were unable to assess whether CIV lead to a shorter length of stay compared to IIV. Initially, we hypothesized patients receiving CIV would achieve therapeutic levels faster, achieve faster clinical response, and therefore be discharged from hospital sooner. However, we found that although patients were clinically stable, discharge or transfer to another facility was often delayed for reasons other than vancomycin therapy.
4.11 Future Work

A prospective, randomized controlled trial comparing CIV versus IIV should be performed to validate the safety and efficacy of CIV versus IIV. Doing so would also allow us to ensure that vancomycin peak, trough, and $C_{ss}$ levels are ordered in accordance with institutional guidelines. Furthermore, the prospective study would allow us to be able to explore and potentially identify the $AUC_{24h}$ breakpoint for nephrotoxicity.

Although this study tried to assess the safety of CIV versus IIV in the outpatient setting, there were only a limited number of patient records available. Some patient records were not complete and missing serum creatinine values, thus preventing the assessment of nephrotoxicity. In 2016, SHSC-BC started the intravenous antibiotic therapy (IVAT) clinic, a service dedicated to patients receiving intravenous antibiotics as outpatients. Patients discharged on vancomycin have their serum creatinine and vancomycin levels forwarded to IVAT where an Infectious Diseases physician will monitor the patient and make any changes if necessary. This may provide a central database to assess the safety and efficacy of CIV as an outpatient in the future.

Additional work should also be completed to further explore the relationship between steady state trough for patients receiving IIV and $AUC_{24h}$. Our study identified a potentially linear relationship between $AUC_{24h}$ and serum vancomycin trough, which requires prospective validation.

4.12 Conclusion

This multicentre, matched, retrospective cohort study determined patients receiving CIV were less likely to develop nephrotoxic risk and renal injury compared to IIV. Patients receiving CIV were approximately 40-45% less likely to experience nephrotoxicity, even after controlling for other potential factors that may influence nephrotoxicity. We did not see any differences between CIV and IIV in clinical cure, microbiological cure, or incidence of other vancomycin-associated adverse events. Furthermore, patients receiving CIV achieved therapeutic levels in less time, required fewer vancomycin levels drawn, and required fewer dose adjustments than IIV. Additional work evaluating the outpatient safety of CIV is needed.
References


5 Appendices

5.1 RIFLE Criteria [1]

- **Risk**: Increased serum creatinine by 50% or a reduction in creatinine clearance by >25%.
- **Injury**: Doubling of serum creatinine or a reduction in creatinine clearance by >50%.
- **Failure**: Tripling of serum creatinine or a reduction in creatinine clearance by 75% or serum creatinine ≥ 4mg/dL (350µmol/L) in the setting of an acute increase of at least 0.5mg/dL (44µmol/L).
- **Loss**: Persistent acute renal failure, defined as a complete loss of kidney function for >4 weeks.
- **End stage kidney disease**: Complete loss of kidney function for >3 months.
5.2 Nephrotoxic Drugs, Drugs causing acute interstitial nephritis, ototoxic drugs, antibiotics with similar spectrum of activity to vancomycin

<table>
<thead>
<tr>
<th>Nephrotoxic Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Antivirals (acyclovir, foscarnet, ganciclovir)</td>
</tr>
<tr>
<td>• Aminoglycosides</td>
</tr>
<tr>
<td>• Amphotericin</td>
</tr>
<tr>
<td>• Angiotensin converting enzyme (ACE) inhibitors</td>
</tr>
<tr>
<td>• Angiotensin receptor blockers (ARBs)</td>
</tr>
<tr>
<td>• Cisplatin</td>
</tr>
<tr>
<td>• Diuretics (thiazides, furosemide, triamterene)</td>
</tr>
<tr>
<td>• Drugs of abuse (coca ine, heroin, ketamine, methadone, methamphetamine)</td>
</tr>
<tr>
<td>• Gold therapy</td>
</tr>
<tr>
<td>• Haloperidol</td>
</tr>
<tr>
<td>• Methotrexate</td>
</tr>
<tr>
<td>• Non-steroidal anti-inflammatory drugs (NSAIDs)</td>
</tr>
<tr>
<td>• Pamidronate</td>
</tr>
<tr>
<td>• Pentamidine</td>
</tr>
<tr>
<td>• Quinine</td>
</tr>
<tr>
<td>• Radiocontrast dye</td>
</tr>
<tr>
<td>• Sulfonamides</td>
</tr>
<tr>
<td>• IV Voriconazole</td>
</tr>
<tr>
<td>• Zoledronate</td>
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<table>
<thead>
<tr>
<th>Drugs Causing Acute Interstitial Nephritis (not listed above)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Allopurinol</td>
</tr>
<tr>
<td>• Anticonvulsants (phenytoin, carbamazepine, phenobarbital)</td>
</tr>
<tr>
<td>• β-lactam antibiotics (penicillins, cephalosporins, and carbapenems)</td>
</tr>
<tr>
<td>• Fluoroquinolones</td>
</tr>
<tr>
<td>• Gastrointestinal medications (proton pump inhibitors, H₂ receptor antagonists)</td>
</tr>
<tr>
<td>• Rifampin</td>
</tr>
<tr>
<td>• Isoniazid</td>
</tr>
<tr>
<td>• Macrolides</td>
</tr>
<tr>
<td>• Tetracyclines (doxycycline, minocycline, tetracycline)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ototoxic Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Aminoglycosides</td>
</tr>
<tr>
<td>• Cisplatin</td>
</tr>
<tr>
<td>• Diuretics (thiazide diuretics, furosemide)</td>
</tr>
<tr>
<td>• Macrolides (erythromycin)</td>
</tr>
<tr>
<td>• Quinin</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Antibiotics with Similar Spectrum of Activity to Vancomycin</th>
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</thead>
<tbody>
<tr>
<td>• Daptomycin</td>
</tr>
<tr>
<td>• Linezolid</td>
</tr>
<tr>
<td>• Tigecycline</td>
</tr>
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</table>
5.3 APACHE II score and approximate mortality[2]

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<thead>
<tr>
<th>APACHE II Score</th>
<th>Approximate Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 4 points:</td>
<td>4% non-op, 1% post-op</td>
</tr>
<tr>
<td>5 to 9 points:</td>
<td>8% non-op, 3% post-op</td>
</tr>
<tr>
<td>10 to 14 points:</td>
<td>15% non-op, 7% post-op</td>
</tr>
<tr>
<td>15 to 19 points:</td>
<td>24% non-op, 12% post-op</td>
</tr>
<tr>
<td>20 to 24 points:</td>
<td>40% non-op, 30% post-op</td>
</tr>
<tr>
<td>25 to 29 points:</td>
<td>55% non-op, 35% post-op</td>
</tr>
<tr>
<td>30 to 34 points:</td>
<td>Approx 73% both</td>
</tr>
<tr>
<td>35 to 100 points:</td>
<td>85% non-op, 88% post-op</td>
</tr>
</tbody>
</table>
5.4 Pharmacokinetic calculations

5.4.1 AUC_{24h} for patients receiving CIV

- \( \text{AUC}_{24h} = \frac{\text{Total Dose in 24h}}{\text{Clearance}} \)
  - Since Clearance = \( k_e \times V_d \)
  - Total daily dose with CIV = \( k_0 \times 24 \)
  - \( C_{ss} = \frac{k_0}{Cl} = \frac{k_0}{k_e V_d} \)

- Therefore, \( \text{AUC}_{24h} \)
  
  = \( \frac{\text{Total daily dose in 24h}}{k_e V_d} \)
  = \( \frac{k_0 \times 24}{k_e V_d} \)
  = \( \frac{k_0}{k_e V_d} \times 24 \)
  = \( C_{ss} \times 24 \)

5.4.2 Elimination constant (\( k_e \))

\[ C_t = C_0 e^{-k_e t} \]

- \( C_t \) = concentration at time \( t \)
- \( C_0 \) = initial concentration
- \( k_e \) = elimination constant
- \( t \) = time (hours) between \( C_0 \) and \( C_t \)

\[ k_e = \frac{\ln C_t}{C_0} \]

5.4.3 Volume of distribution (\( V_d \))

\[ V_d = \frac{\text{Dose}}{k_e \times t'} \times \frac{1 - e^{-k_e t'}}{[C_{max}^{\text{ext}} - (C_{min}^{\text{ext}} \times e^{-k_e t'})]} \]

- \( V_d \) = volume of distribution (L/kg)
- \( k_e \) = elimination constant
- \( t' \) = duration of infusion (hours)
- \( C_{\text{max}}^{\text{ext}} \) = extrapolated peak concentration = \( (C_{\text{obs max}}^{\text{ext}} / e^{-k_{t\text{max}}}) \)
  - \( C_{\text{obs max}}^{\text{ext}} \) = observed maximum concentration
  - \( t_{\text{max}} \) = time to observed maximum concentration post infusion
- \( C_{\text{ext min}} = \) extrapolated trough concentration = \( C_{\text{ext max}} e^{-k(\tau-t')} \)
  
  - \( \tau = \) dose interval (hours)

5.4.4 24 hour area under the curve

\[
AUC_{24h} = \frac{\text{Total daily dose in mg}}{V_d \times k_e}
\]

5.4.5 Cockcroft-Gault equation [3]

\[
CrCl \left( \frac{\text{mL}}{\text{min}} \right) = \frac{(140 - \text{age}) \times \text{body weight (kg)} \times 1.23}{\text{Serum creatinine (imol/L)}} \times 0.85 \text{ for women}
\]

5.4.6 Rodvold nomogram[4]

\[
\text{Vancomycin Clearance} \left( \frac{\text{mL}}{\text{min}} \right) = (CrCl \times 0.79) + 1.57
\]

\[
\text{Vancomycin Clearance} \left( \frac{L}{h} \right) = [(CrCl \times 0.79) + 1.57] \times 0.06
\]

\[
AUC_{24h} = \frac{\text{Total daily dose in mg}}{[(CrCl \times 0.79) + 1.57] \times 0.06}
\]
## 5.5 Complete list of Gram-positive pathogens

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>CIV</th>
<th>IIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobic spore forming bacilli</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Anaerococcus murdochii</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Bacillus megaterium</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Bacillus spp.</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Clostridium perfringens</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Clostridium tertium</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Corynebacterium jeikeium</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Corynebacterium striatum</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Corynebacterium tuberculostearicum</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Diphtheroid bacilli</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Finegoldia magna</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Gemella spp.</td>
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<td>1</td>
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<tr>
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