Official Title: Safety and Outcomes Associated With Continuous Versus Intermittent Infusion Vancomycin in Outpatient Parenteral Antibiotic Therapy: a Prospective, Randomized Trial
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Study Title: Safety and outcomes associated with continuous versus intermittent infusion vancomycin in outpatient parenteral antibiotic therapy: a prospective, randomized trial

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Background, Rationale and Context

The 2020 American Society of Health-System Pharmacists, Infectious Diseases Society of America, Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists Guidelines for Therapeutic Monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections endorse the monitoring of vancomycin by area under the curve (AUC) to minimum inhibitory concentration (MIC) ratio per 24 hours (AUC/MIC)[1]. The AUC/MIC has been determined to accurately predict treatment efficacy and decrease the prevalence of adverse drug reactions in comparison to trough-based monitoring[2-10]. In respect to these recommendations, AUC/MIC monitoring is the standard of care in the inpatient setting at our institution. However, due to complications with home nursing visits and feasibility, this method of monitoring is not well established in the outpatient setting. This is secondary to the requirement of appropriately timed vancomycin peak and trough concentrations, and the subsequent calculation of the AUC/MIC. One proposed method of accurately monitoring AUC/MIC during outpatient therapy is to convert patients to continuous infusions (CI) of vancomycin instead of intermittent infusions (II). One random level of vancomycin is sufficient to calculate the AUC during a CI of vancomycin. This is performed by multiplying the random level by 24 hours to obtain an AUC/MIC. In regard to safety, the use of CI vancomycin has been studied in patients in intensive care units, and has been associated with lower rates of nephrotoxicity, but no benefit in mortality or treatment success[11-17]. Despite the anticipated benefit of easier AUC monitoring and less nephrotoxicity, the comparison of treatment efficacy and safety of CI versus II vancomycin in the outpatient setting is limited.

To date, there are only three trials that have evaluated the safety of CI vancomycin in outpatients. In 2008, Ingram et al. performed a retrospective cohort study of patients receiving CI vancomycin to determine risk factors for vancomycin-associated nephrotoxicity. The authors concluded that the following variables were positively associated with new-onset nephrotoxicity: steady state vancomycin levels greater-than or equal-to 28, loop diuretics, aminoglycosides, and hypertension[18].

In 2012, Dubee et al. prospectively observed 60 patients receiving high-dose CI vancomycin for prosthetic hip infections. The target serum vancomycin level was 30 to 40 mcg/mL, which would correlate with an AUC of 720 to 960[19]. This is above the guideline-recommended range of 400-600, as AUCs above 600 have been associated with no difference in treatment outcomes, but an increase in nephrotoxicity[10]. The authors concluded that 19 patients experienced nephrotoxicity, defined as a rise in serum creatinine by 50% from baseline, while receiving vancomycin. Of note, 16 of these patients were receiving concomitant nephrotoxic medications[19]. Thus, the outcomes of this trial are limited to higher vancomycin dosing and high prevalence of confounding variables, such as concurrent nephrotoxins.

In 2009, Ingram et al. studied the prevalence of nephrotoxicity between CI and II vancomycin in patients seen by an outpatient parenteral antibiotic therapy (OPAT) clinic in Singapore. The authors noted that there was an increased prevalence of nephrotoxicity in the II group than the CI (23.6% and 11.6%, respectively), but the two groups were not matched in regard to patient characteristics. Overall, the patients in the CI arm had a younger mean age by approximately 10 years (46.7 vs 57.3 years) with less evidence of hypertension (25.9% vs 47.3%), diabetes mellitus (21.4% vs 50.9%), and ACE-inhibitor/ARB use (13.4% vs 41.8%), as well as lower mean serum creatinine (0.71 vs 0.84 mg/dL)[20].

Similarly, two trials have evaluated the efficacy comparing CI and II. In 2004, Vaugant et al. prospectively measured the efficacy of CI versus II in 43 patients with osteomyelitis. Both treatment arms targeted serum vancomycin levels/troughs of 20 to 25 mcg/mL[21]. For those that were receiving trough-based monitoring, this level is above traditional dosing recommendations of 15 to 20 mcg/mL[1,8]. Secondary to this higher target, four patients in the II group and zero in the CI group experienced nephrotoxicity. Treatment failure occurred in two patients in each group[21].

In 2012, Verrall et al. expanded upon these findings by retrospectively reviewing patients receiving CI or II vancomycin in the OPAT setting for any MRSA infection. This study included patients that were treated in accordance with current guideline recommended therapy: vancomycin trough goal of 15 to 20 mcg/mL in the II group, and vancomycin random level of 15 to 25 mcg/mL in the CI group[1]. The authors concluded that a higher rate of clinical failure occurred in the II group than the CI group (30.4% vs 21.3%, respectively). However, there were numerously more patients in the CI group (145 vs 40 patients), and a higher rate of unplanned re-admissions occurred in the II group, which drove this primary endpoint of clinical failure[22].

Thus, to supplement the paucity of data of CI versus II vancomycin in the outpatient setting, the purpose of this study is to evaluate the safety and outcomes associated between the two treatment modalities.

Objectives

The objectives of the study are to assess the risk of vancomycin-associated nephrotoxicity and outcomes associated with CI versus II dosing in the OPAT setting.

Methods and Measures

Design

Prospective, randomized, open-label, single-center trial

Setting

Wake Forest Baptist Health OPAT service

Subjects selection criteria

- **Inclusion Criteria**
  - Adult patients at least 18 years of age
  - Receiving Wake Forest Baptist Health OPAT services
  - Will receive vancomycin therapy from Wake Forest Baptist Health Specialty Home Infusion Pharmacy
  - Planned therapy with vancomycin in the outpatient setting for at least 2 weeks in duration
  - Prescribed vancomycin with a frequency of either every 12 hours or every 8 hours dosing at the time of enrollment
- **Exclusion Criteria**
  - Presence of diseases or conditions known to affect the pharmacokinetics of vancomycin
    - Pregnancy
    - Ascites

    - Burn injury
    - Cystic fibrosis
    - Weight greater-than or equal-to 150 kg
  - Pre-existing leukopenia
    - WBC < 4,000 x 10^3 cells/μL
- **Sample Size**
  Assuming that II vancomycin therapy will be associated with an increase in nephrotoxicity by 15% and a level of significance of 0.05 and 80% power, the sample size needed in each group is 100 patients.

Interventions and Interactions

Patients will be identified during routine care by members of the Infectious Diseases (ID) Consult service C team (ID-C), Specialty Home Infusion Pharmacy, or Wake Forest Baptist Infectious Diseases clinic. Members of the study team will review the electronic medical record (EMR) to apply study criteria for inclusion. Written informed consent will be secured by in-person, non-biased explanation of the study. Study candidates that are currently admitted to the hospital will receive education about the study in his or her hospital room. Study participants that provide written, informed consent will be randomized into either the CI or II group by a random number generator. All patients will receive their first dose of vancomycin as an intermittent infusion.

Inpatient study candidates that are randomized to the CI group will have their total daily cumulative dose of vancomycin converted to a 24-hour intravenous infusion upon discharge. The CI will begin with the first scheduled OPAT dose of vancomycin. Inpatient study candidates that are randomized to the II group will continue their current intravenous dosing upon discharge. Members of the Specialty Home Infusion Pharmacy will ensure vancomycin is dispensed as single or multiple elastomeric balloon pumps depending assigned group. Prior to discharge, the study candidate or caretaker will receive education on how to administer doses of vancomycin per standard of care.

Study candidates that are receiving their first dose of vancomycin in the day hospital after being transferred from the OPAT Clinic, will receive education about the study in his or her Day Hospital room. Outpatient or Day Hospital study candidates randomized to the CI or II group will receive vancomycin dosed according to OPAT team recommendations. Members of the Specialty Home Infusion Pharmacy will ensure vancomycin is dispensed as single or multiple elastomeric balloon pumps depending on assigned group. Prior to discharge, the study candidate or caretaker will receive education on how to administer doses of vancomycin per standard of care.

After enrollment, data will be collected from the EMR, including: demographic information, laboratory data, anthropometry measurements, comorbid or chronic diseases or conditions, concurrent medications, information about the infection, planned duration of therapy, planned dose of vancomycin, results of vancomycin concentrations, and previous and concurrent antibiotic therapy. Data will be recorded using a pre-defined data collection form (RedCap).

After discharge, vancomycin will be monitored as established by the standard procedures of the Specialty Home Infusion Pharmacy and OPAT service. The standard monitoring frequency for vancomycin concentrations is at least weekly for all OPAT patients. If randomized to the CI group, vancomycin random concentrations will be used to guide dosing based on AUC determinations. The CI goal AUC is 400-600 mg x hr/L. If randomized to the II group, vancomycin monitoring will be performed one of two ways, depending on whether the inpatient (pre-discharge) dose of vancomycin was determined by AUC monitoring. If it was, the target vancomycin trough concentration will approximate the trough that corresponded to the dose that resulted in an AUC of 400-600 mg x hr/L. If the discharge dose of vancomycin was not determined by inpatient AUC monitoring, a pre-determined target range will be established based on the indication for vancomycin, typically 15 – 20 mcg/mL for difficult to treat infections. Adjustments of vancomycin doses will be made by pharmacists of the Specialty Home Infusion Pharmacy or providers working on the OPAT service. Other monitoring labs that will be

performed weekly per standard of care include basic metabolic panel and complete blood cell count with differential.

Study participants will follow-up at regularly scheduled OPAT Clinic visits in accordance with routine care. The treating clinician will monitor for signs and symptoms of infection to determine resolution or persistence of disease during these visits per usual care. Data collection for study purposes will occur for the entire duration of vancomycin therapy.

A table illustrating the schedule of events in the study is attached as Appendix 3.

Outcome Measure(s)

- Safety:
    - Nephrotoxicity: Any increase in Scr by 50% from baseline, an increase in Scr by 0.5 mg/dL, or an increase in Scr by 0.3 mg/dL on two consecutive measurements
        - Baseline SCr is defined as the most recent SCr measurement prior to randomization
    - Leukopenia
        - WBC < 4,000 x 10^3 cells/µL
    - Infusion-related reactions
        - Flushing
        - Erythema
        - Rash
        - Red Man Syndrome
    - Serious adverse events
        - FDA, Common Terminology Criteria for Adverse Events (CTCAE), Grade 3 events – severe or medically significant, but not immediately life-threatening events leading to hospitalization or disability
            - Disability means to limit the ability to conduct self-care activities of daily living (bathing, dressing, feeding self, using the toilet, taking medications, and not bedridden)
        - FDA, CTCAE, Grade 4 events – life-threatening adverse events requiring urgent intervention
- Total number of serum vancomycin concentrations during treatment period
- Number of serum vancomycin measurements within therapeutic range
    - CI goal
        - AUC/MIC 400 – 600 mg x hr/L (a vancomycin random within 16.7 and 25.0 mcg/mL will correlate with this range)
    - II goal
            - If inpatient dose was determined by AUC monitoring: A vancomycin trough that is within 3.0 mcg/mL of the trough that correlated with a therapeutic AUC based on inpatient monitoring.
        - If inpatient dose was not determined by AUC monitoring or vancomycin was initiated as outpatient: A vancomycin trough of 10.0 – 20.0 mcg/mL
- Treatment Success
    - Resolution of signs and symptoms associated with the infection
        - Systemic signs and symptoms of infection
            - Fever (100.4 degrees Fahrenheit sustained over 1 hour or a single measurement of 101 degrees Fahrenheit or more)
            - Elevated WBC greater than 12.0 cells x 10^3 cells/µL
            - Chills

        - Localized signs and symptoms of infection
            - Erythema at the site of infection
            - Drainage at the site of infection
            - Fluctuance
            - Heat or localized warmth
            - Tenderness on palpation
            - Swelling or induration
        - No need for additional induction therapy beyond the planned end date
            - Induction therapy is defined as the initial antibiotic regimen prescribed to treat the patient's infection, typically 6-8 weeks of intravenous therapy

- Treatment Failure
    - Persistence, new onset, or worsening local or systemic signs and symptoms of infection
    - Amputation due to progression of disease within 90 days after the end of induction or consolidation antibiotics
    - Breakthrough positive cultures with the same causative pathogen while receiving or at the conclusion therapy with vancomycin. This includes those undergoing two-stage joint replacements that have repeat culture of the same causative pathogen prior to the placement of new prosthetic material.
    - The need for additional antibiotic use for no response or worsening after improvement
    - Patients will not be considered as treatment failure if they require oral consolidation or long-term suppressive antibiotic therapy after the completion of vancomycin.

Analytical Plan

Results will be analyzed initially using descriptive statistics. Comparison between groups will be done using Chi square test for categorical data, and Student t-tests or ANOVA for continuous variables. Safety outcomes will be evaluated using an intention to treat (ITT) population and clinical outcomes will be evaluated using a modified intention to treat (mITT) population. The ITT population will be all patients that receive at least one dose after randomization. The mITT group will consist of those that completed the planned treatment course. Other inferential statistical analyses will be conducted as appropriate.

Human Subjects Protection

The primary investigators will be responsible for maintaining the integrity of all data. Only study investigators will have access to secured data for the study.

Subject Recruitment Methods

Study candidates will primarily be identified by members of the ID-C, Specialty Home Infusion Pharmacy, and Infectious Diseases Clinic staff during routine care. Key members of the ID-C, Specialty Home Infusion Pharmacy, and Infectious Diseases Clinic staff are study investigators. Study candidates may be identified during Infectious Diseases Clinic visits if the initiation of therapy with vancomycin is warranted in the outpatient setting.

As all patients with osteomyelitis, prosthetic joint infections, endocarditis, epidural abscesses, and complicated MRSA bacteremia have an equal opportunity to require therapy with vancomycin, women and minorities have equal access to participation in this study.

The privacy of potential subjects during recruitment will be protected by HIPAA requirements, as the members of the study team are the members of the treatment teams. Collection and documentation of study enrollment or decline will be saved on a password-protected file and will be deleted after data analysis is finalized.

Informed Consent

Signed informed consent will be obtained from each subject. A study investigator will obtain informed consent from each patient while they are receiving care at WFBMC. This includes, but is not limited to, the patient's hospital room, Day Hospital room, or Infectious Diseases Clinic location.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection and analysis subject identifying information will be destroyed, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

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Appendix

9.30.2020

1. Data collection form
2. Informed consent form
3. Schedule of events tables
4. Copies of each questionnaires or surveys that will be used