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DATE RECEIVED: ***04/11/2025*** *DATE APPROVED:* ***04/11/2025***

FILE NUMBER: ***#25-055***

APPLICATION FOR STATISTICAL CONSULTING

LAST NAME**:** Erdman

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YOUR PRIMARY POSITION AT PURDUE: Faculty

Other:

(if a student) MAJOR PROFESSOR LAST NAME: FIRST NAME:

PHONE NUMBER:

MAJOR PROFESSOR CAMPUS ADDRESS (BLDG & DEPT): /

MAJOR PROFESSOR EMAIL:

HOW DID YOU FIND US: Recommendation of a colleague

LIST STATISTICS COURSES TAKEN AND STATISTICAL COMPUTING EXPERIENCE: Introductory stats....many years ago

STAGE OF RESEARCH: Analysis (all data have been collected)

IF DESIGN STAGE IS COMPLETE, WAS A STATISTICIAN CONSULTED FOR DESIGN? No

PREVIOUS CONSULTANT – INSTITUTION/DEPARTMENT:

ESTIMATED NUMBER OF CONSULTING HOURS NEEDED THIS SEMESTER: <5 hours

EXPECTED COMPLETION DATE OF PROJECT: 4/30/2025

IMPORTANT DEADLINE OR DUE DATES RELATED TO YOUR PROJECT:

THE RESULTS OF THIS RESEARCH WILL PROBABLY BE PUBLISHED AS:

Journal Article

IS THIS RESEARCH SUPPORTED BY A GRANT OR CONTRACT? No

If so, give grant/contract title:

GIVE A BRIEF DESCRIPTION OF YOUR RESEARCH INCLUDING:

PURPOSE:

The optimal strategy for dosing and monitoring vancomycin continues to evolve. A vancomycin 24-hour steady-state area under the concentration-time curve/minimum inhibitory concentration (AUC/MIC) of ≥ 400 has been associated with positive clinical outcomes, while an AUC/MIC > 600-700 has been associated with increased risk of nephrotoxicity. The 2009 vancomycin dosing guidelines recommended target trough concentrations between 10-20 mcg/mL depending on infection; however, recent pharmacokinetic data suggest that most patients can achieve target AUC/MIC with trough concentrations < 15 mcg/mL. While existing literature has demonstrated reduced nephrotoxicity with AUC-guided dosing, there are limited data evaluating efficacy and other clinical outcomes. Therefore, this study compared the clinical efficacy of vancomycin using trough-guided (TGD) versus AUC-guided dosing (AGD) in patients with confirmed methicillin-resistant Staphylococcus aureus bacteremia.

DESCRIPTION OF VARIABLES TO BE MEASURED:

This was a single-center, retrospective, observational, quasi-experimental, non-inferiority study conducted at Eskenazi Health, a 333-bed safety-net, tertiary care, teaching hospital where vancomycin dosing is performed using a pharmacy-to-dose protocol. The original vancomycin pharmacy-to-dose protocol was based on trough-guided dosing but transitioned to AUC-guided dosing using the trapezoidal rule on October 14, 2019. The pre-implementation trough-guided dosing group (TGD) consisted of patients that were initiated on vancomycin using the trough-based dosing strategy between October 1, 2016 and September 30, 2018. The post-implementation AUC-guided dosing group (AGD) consisted of patients who were initiated on vancomycin using the AUC-based dosing strategy between October 14, 2019 and November 30, 2021. The date range selected for the pre-implementation group does not immediately precede the date range for the post-implementation group because some pharmacists were employing more conservative dosing based on available literature (targeting troughs <15 mcg/mL for gram positive infections caused by organisms other than MRSA) prior to the institution officially switching from trough-based dosing to AUC-based dosing. Therefore, the research team purposely included a washout period of one year between groups to minimize the impact on study results.

The primary outcome was microbiological success defined as the achievement of negative blood cultures within 7 days of vancomycin initiation. Microbiological failure was defined as persistently positive blood cultures on vancomycin therapy 7 days after the first positive blood culture or 7 days after achieving adequate source control, whichever occurred later. Infections that generally did not require additional intervention outside of antibiotic treatment to achieve adequate source control (e.g., pneumonia, cellulitis) were categorized as achieving source control, while those patients with infections requiring source control (e.g., abscesses prosthetic joint infections, etc.) that were not suitable surgical candidates were classified as not achieving source control.

Secondary outcomes included the number of patients who achieved therapeutic vancomycin concentrations with the first set of steady-state vancomycin serum concentrations (TGD: trough goal 10-20 mcg/mL; AGD: AUC/MIC goal 400-600), daily vancomycin dose, duration of vancomycin therapy

(included total planned duration of vancomycin course inclusive of outpatient administration of antibiotics following discharge), the incidence of nephrotoxicity defined as an increase in SCr by ≥ 0.5 mg/dL from baseline or an increase by ≥ 50% of baseline SCr on two consecutive measurements that can be reasonably attributed to vancomycin (received minimum of 48 hours of vancomycin therapy)1, hospital length of stay, 30-day infection-related hospital readmission, and all-cause in-hospital mortality.

RESEARCH QUESTIONS THAT YOU WANT TO ADDRESS USING STATISTICAL METHODS:

Is AUC-guided vancomycin dosing non-inferior to trough-guided dosing in terms of acieving therapeutic concentrations and efficacy.

STATISTICAL ISSUES:

The journal article reviewer stated " I suggest to harmonize the statistical hypothesis (non-inferiority) and the corresponding statistical method of testing as well as the sample size calculation. Now in the article, it is looks more like testing of a statistical superiority hypothesis." and gave this supporting information.

Non-inferiority trials (NITs) are an extension of conventional superiority trials, but they use another statistical hypothesis. Non-inferiority trials determine if the new intervention is “not substantially worse” than the comparator based on the confidence interval of this difference not including a predefined unfavourable difference in outcomes—the non-inferiority margin Δ. Non-inferiority has sometimes been erroneously used when the difference between two treatments is inconclusive without reference to a non-inferiority margin. An inconclusive outcome simply means that no statistically significant difference was seen between the two treatments and relates to statistical superiority testing.

Aim of superiority trials (statistical superiority hypothesis) is to determine whether a new intervention is superior to the comparator, aim of non-inferiority trials is to demonstrate that the new intervention is no worse than the comparator by more than a prespecified, small amount. This amount is known as the non-inferiority margin, or delta (Δ). The null hypothesis (H0) of superiority trials asserts that there is no true difference between the interventions, and the alternative hypothesis (HA) states that there is a difference between the interventions. NITs have a H0 that the new intervention is worse than the comparator by more than − Δ (it is inferior). The HA to be proven is that the new intervention is inferior to the comparator by less than − Δ (it is not inferior). For more details, see, for example, article [D'Agostino Sr RB, Massaro JM, Sullivan LM. Non-inferiority trials: design concepts and issues – the encounters of academic consultants in statistics. Stat Med. 2003;22(2):169–86] or

https://pmc.ncbi.nlm.nih.gov/articles/PMC7808096/pdf/main.pdf.

I need some assistance in achieving what they asked in the stats section.

ADDITIONAL INFORMATION YOU THINK WOULD BE HELPFUL:

ATTACHMENTS:

Attachment in Clients Folder