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Swab Testing to Optimize Pneumonia treatment with empiric Vancomycin (STOP-Vanc)

Statistical Analysis Plan

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Introduction

Methicillin-resistant Staphylococcus aureus (MRSA) is a critical antimicrobial resistant threat. Community-acquired pneumonia (CAP) is a major driver of hospital antibiotic use. However, MRSA is an infrequent cause of community-acquired pneumonia (CAP), accounting for less than 1% of cases. Despite this, MRSA is a frequently feared cause of CAP, which leads to the frequent use of vancomycin, an anti-MRSA antibiotic, in empiric CAP treatment. The use of vancomycin is unfortunately associated with a high risk for toxicity and serious adverse events. Furthermore, vancomycin is a costly antibiotic to use in the hospital as it requires careful monitoring due to its narrow therapeutic range and high risk of toxicity. Therefore, reducing inappropriate use of vancomycin in patients with CAP has the potential to improve patient outcomes while at the same time providing overall cost savings. There is growing data to support the use of MRSA nasal swabs as a screening method to guide de-escalation of vancomycin use in CAP. Furthermore, the use of MRSA detection in nasal swabs is now consistent with guideline-based management of CAP.

This document describes the statistical analysis plan for a single center, pragmatic, randomized clinical trial designed to evaluate the impact of MRSA nasal swab PCR detection along with antimicrobial guidance in reducing inappropriate vancomycin usage in CAP patients. This document has been prepared prior to final data collection and unblinding. It is hypothesized that implementation of screening in conjunction with antimicrobial stewardship guidance on interpretation of the results will lead to reduced use of vancomycin. Furthermore, as secondary aims, it is anticipated that a reduction in vancomycin-associated adverse events and an overall cost-savings will be observed, all without increasing mortality or hospital readmissions.

Population and design considerations

Study Population:

Adult (age greater than or equal to 18) patients admitted/transferred to the Vanderbilt University Medical Center (VUMC) Medical Intensive Care Unit (MICU) who are receiving vancomycin for CAP. All eligible patients will be included and there will be no selection based on sex, race, weight, or other clinical factors. Patients will automatically be considered for enrollment either upon transfer to the MICU with an order for "pharmacy to dose vancomycin" already in place, or if an order for vancomycin and/or a consult for "pharmacy to dose vancomycin" is placed (within 24 hours of admission to unit) for a patient located in the MICU, and if they have not already received topical nasal decolonization during the hospitalization. The reasons for ineligibility of patients screened but not enrolled will be recorded.

Inclusion criteria:

- Adult (age greater than or equal to 18) patients admitted/transferred to the VUMC MICU from the VUMC Emergency Department or from a hospital floor within 48 hours of admission.
- Suspicion for pneumonia on admission (defined as an indication for antibiotics of "respiratory infection" and/or an order for a respiratory culture i.e., sputum culture, tracheal aspirate culture, or bronchoalveolar lavage (BAL) culture).
- No topical nasal decolonization during hospitalization prior to collection of MRSA nasal swab PCR.
- Must match both of the following in either order:

- The patient has been admitted to and physically located in the MICU.
- The patient has received a continuing vancomycin order, or a pharmacokinetics consult for a continuing vancomycin order, no later than 24 hours following their physical admission to the MICU.

Exclusion criteria:

- Hospital stay of longer than 48 hours prior to MICU admission.
- Known to be a prisoner.

Study Design:
This is a single center, pragmatic, randomized clinical trial (pRCT) examining whether reporting the results of a negative rapid PCR back to the provider via a pager alert results in decreased vancomycin utilization for critically ill adults with community-acquired pneumonia when compared with usual care.

Randomization:
For patients who meet the study criteria, as outlined above, and are randomized to the intervention arm of the study, a MRSA nasal swab will be collected upon admission to the MICU prior to topical nasal decolonization and a PCR test will be ordered to be run on the collected MRSA nasal swab (no nasal swab will be collected on patients enrolled in the control arm). Patients will be randomized in a 1:1 fashion on an individual patient level.

Sample Size Considerations:
The method used for sample size estimation is based on a traditional univariate proportional odds model. The actual primary analysis is based on a longitudinal proportional odds model that makes use of hourly patient status.

A 24-hour reduction is considered clinically meaningful.

To overcome challenges with mortality, which is estimated to be 22% within 8 days, the primary outcome, 'Vancomycin-free hours alive', will be defined as the number of hours alive and free of the use of vancomycin within the first seven days of study enrollment. This is not a quantity that is calculated on raw data because of deaths but is derived from the longitudinal model described below. The result is summarized as a treatment difference in mean Vancomycin-free hours alive for specific covariate settings (p-values are the same for all covariate settings since treatment is not allowed to interact with covariates). The result will also be summarized by an odds ratio for the hour-to-hour state transitions, from the proportional odds longitudinal model.

In those who do not die, it is estimated that the relative frequencies for all possible outcomes will be equal to 0.023, 0.008, 0.019, 0.027, 0.095, 0.125, 0.224, 0.262 (for 0 to 7 Vancomycin-free days). Given this distribution, and an assumption of 22% mortality, an overall 24-hour increase in mean 'Vancomycin-free hours alive' would be associated with a common odds ratio for a univariate proportional odds logistic model of about 2.2. To detect this difference with 90% power would require about 106 subjects per study group.

Near the midpoint of the trial, we determined a subset of patients (approximately 12% while being blinded to results) who had a MRSA PCR swab ordered prior to enrollment, and another subset of patients (approximately 3%) who had been co-enrolled in a similar VUMC study evaluating vancomycin use. As these two populations could influence vancomycin use in both the control and intervention arms of the current study, we increased the sample size to account for this contamination, plus one additional patient to account for an instance of mis-enrollment where the patient did not have an order placed for vancomycin. Based on current incidence rates, the estimated sample size to account for these groups would be 246 patients, with 123 patients per arm. However, as the final percent contamination of these two subgroups within the study's patient population may fluctuate over the remainder of the study period, additional patients will be enrolled as appropriate until the lowest enrolled arm reaches 106 patients in the adjusted cohort, up to a maximum of 300 patients.

Interventions

a. Control group: Enrolled patients in which no MRSA nasal swab is collected and PCR is not run.
b. Intervention group: Enrolled patients in which the MRSA nasal swab PCR will be run and once the MRSA nasal swab PCR has been completed, the results will be available in the EMR along with antimicrobial stewardship program guidance. For patients in the study group with a negative MRSA nasal swab PCR, a pager alert will be sent to the patient's primary team. The pager alert will inform the provider of the negative test result and will direct them to the result in the EMR where they will receive further clinical guidance recommending the provider consider discontinuing vancomycin. In addition to the direct, instantaneous antimicrobial stewardship guidance to be delivered through the EMR as outlined above, general education about the use of MRSA nasal swab PCR testing to guide de-escalation of empiric vancomycin will be provided by the MICU pharmacist when a patient with a negative MRSA nasal swab PCR is continued on vancomycin.

Endpoints

Primary Endpoint

The primary outcome is ordinal 3-level patient status assessed on 168 consecutive hours, with the ordinal status levels being alive and not on Vancomycin, alive and on Vancomycin, or dead. The statistical model explicitly considers death as a negative outcome that is a terminal event (absorbing state in state transition model terminology). The underlying statistical parameter representing the treatment effect is an odds ratio (OR) for staying or transitioning to states given the previous day's state. An OR greater than 1.0 represents higher odds of Vancomycin or death and higher odds of death conditional on the previous day's state (which can only be one of the first two of the three possible states). The OR is translated to clinical restatements of the analysis model as follows (p-values from these other estimands are identical to the p-value from the underlying OR). The ordinal longitudinal transition model directly provides transition probabilities, and the law of total probability is used to convert these to unconditional probabilities (state occupancy probabilities - SOPs) such as the probably of being alive and Vancomycin-free on the 48th hour. The SOPs are summed over hours to estimate mean time in

state, which is used to provide the estimate of the treatment difference in the mean number of Vancomycin-free hours alive, which will be the first estimate reported.

Secondary Endpoint(s)
There are two prespecified secondary outcomes for this trial.

Time Alive off Vancomycin: The number of hours out of the 168 hours (7 days) following enrollment in the trial that the patient is alive and not receiving vancomycin. Time receiving vancomycin will be defined as the difference from time of administration of the first dose of vancomycin to time of administration of the last dose of vancomycin. If the patient was discharged prior to study day 7 and received vancomycin within 24 hours of discharge then the total duration of vancomycin will be calculated based on the anticipated last day of vancomycin at the time of discharge or else by using study day 7 as an end point, whichever is sooner.

30-day all-cause mortality: Defined as mortality within 30 days with date of study enrollment as day 0.

Exploratory Endpoint(s)
There are multiple prespecified exploratory outcomes for this trial.

Length of stay (LOS): Defined as the difference in days from date of presentation to VUMC to the date of discharge, inclusive of first and last dates.

Total ICU LOS: Defined as the difference in hours from time of admission to MICU to transfer out of MICU (summed if multiple separate transfers to MICU during the same hospitalization).

Total duration of antibiotic exposure: Defined as the difference in days from time of first dose of any oral or IV antibiotic to the last dose of antibiotics, inclusive of first and last dates. If the patient was discharged prior to study day 14 and received antibiotics within 24 hours of discharge then the total duration of antibiotics will be calculated based on the anticipated last day of antibiotics at the time of discharge or else by using study day 14 as an end point, whichever is sooner.
Total duration of parenteral antibiotic exposure: Defined as the difference in days from time of first dose of any parenteral antibiotic to the last dose of parenteral antibiotics, inclusive of first and last dates. If the patient was discharged prior to study day 14 and had received parenteral antibiotics within 24 hours of discharge then the total duration of parenteral antibiotics will be calculated based on the anticipated last day of parenteral antibiotics at the time of discharge or else by using study day 14 as an end point, whichever is sooner.

Ventilator-free days: Defined as the number of days out of the 14 days following enrollment in the trial that the patient is alive and not intubated.

Total cost of vancomycin use: Defined as the estimated cost of vancomycin administration as a composite of cost of drug, cost of associated laboratory testing, and cost of pharmacy services required to provide dosing.

AKI: Defined as an increase in creatinine to ≥ 1.5 times the reference creatinine level or an increase by ≥ 0.3 mg/dL within 14 days of study enrollment. Excludes patients who have end stage renal disease (ESRD) prior to study enrollment.

Receipt of any alternative non-vancomycin anti-MRSA pneumonia antibiotics: Defined as receipt of linezolid or ceftaroline during hospitalization (daptomycin excluded given inappropriate antibiotic selection for pneumonia).

In-hospital all-cause mortality: Defined as mortality at any point during the hospital stay prior to discharge.

Predictive value/concordance with final culture-based results: Among patients with both a MRSA nasal swab PCR and a respiratory culture at any point from admission to 7 days after study enrollment, this outcome is defined as the percentage of patients with a positive MRSA nasal swab PCR who also had any respiratory culture during the first 7 days after study enrollment that was positive for MRSA (Positive Predictive Value) and the percentage of patients with a negative MRSA nasal swab PCR who also had any respiratory culture during the first 7 days after study enrollment that was negative for MRSA (Negative Predictive Value).

Implementation Endpoints
Time from collection of swab to results being available in EHR

Fidelity Endpoint
Fidelity of Obtaining Nasal Swab
Fidelity of Running and Reporting PCR Results
Fidelity of Paging Alert to Team

Analysis dataset
The analysis for the trial will use an intent-to-treat approach to answer the effectiveness question posed. That is, participants will be evaluated by treatment group as assigned regardless of what was delivered. All eligible participants will be included.

Statistical Approach
Our initial analysis will be descriptive in nature, summarizing information that characterizes the cohort and the outcomes. Then, we will proceed with inferential analysis to answer the main study question. Then, we will compare the secondary endpoints between study groups.

Descriptive Analysis
To characterize the study sample, baseline demographic and clinical data will be described overall and by group. Categorical variables will be described using frequencies and proportions, and continuous variables will be described using medians and interquartile ranges. Missingness will be reported for each variable. Graphical summaries using box plots, violin plots, and/or histograms may be used to describe the data graphically. At a minimum, the following variables will be described at time of enrollment:

- Encounter ID (patients could be re-enrolled if they have a second or multiple admissions; each admission should be treated separately)
- Age (years)
- Sex (male, female, unknown)
- Race (African American, Asian/Pacific Islander, Caucasian, Multiple, Native American, Other, Unknown)
- Ethnicity (Hispanic, Non-Hispanic, Unknown)
- Height (m)
- Weight (kg)
- BMI
- Elixhauser comorbidity index
- Pre-existing chronic kidney disease (CKD)
    - Baseline CKD
    - Reference Creatinine - Defined as the most recent creatinine obtained since admission but prior to the administration of the first dose of vancomycin. If no value exists, then the most immediate creatinine following the administration of vancomycin will be used.
- End stage renal disease (ESRD)
- Immunocompromised/immunosuppressed
    - HIV
    - Solid organ transplant recipient
    - Stem cell transplant recipient
- Severity of illness
    - SOFA score
    - Requirement for supplemental oxygen and/or intubation
- Diagnostic microbiological workup
    - Number of blood cultures, respiratory cultures, and other respiratory pathogen specific tests ordered per person

We will describe all of the outcome variables overall and grouped by study arm using the same approach as for the demographic data. Summary statistics and graphical representations may be displayed, and missingness will be reported for each variable.

No statistical comparisons between groups will be done for this descriptive analysis. Please note, showing descriptive statistics stratified by treatment groups that were randomized can be easily misinterpreted, as all apparent imbalances are by definition due to chance. Descriptive statistics of all-comers need to be emphasized in randomized studies.

Main Analysis

Primary and secondary outcomes will be analyzed using an intention-to-treat analysis. The primary analysis will use a first-order Markov ordinal longitudinal proportional odds (PO) state transition model with three levels of patient status assessed hourly for 168 hours as described under *Primary Endpoint* above. This model places death as the worst outcome and does not need to code death numerically. A traditional approach of using Vancomycin-free hours alive with death coded as –1 has interpretation problems (and does not handle missing data) and neither means (because of the arbitrariness of –1) nor medians (because of excessive ties in the data) are

adequate summary statistics. The underlying transition model is a partial PO model, *partial* because the effect of time is allowed to vary with the ordinal state being predicted. Put another way, Vancomycin may be used earlier, and deaths occur later, and it is important for the model not to have restrictions on how the various events unfold over time. The model is adjusted for baseline covariates. The within-patient correlation structure in the 3-level statuses is flexibly handled by a Markov process. "First order" means that each transition is conditional only on the previous day's state and not statuses that are earlier. The partial PO model will assume PO for all other effects including treatment.

Letting the outcome variable on day t be denoted by Y(t) with levels 0, 1, 2 (alive & Vancomycin-free, alive & on Vancomycin, dead), and letting expit denote the inverse logit transform, the ordinal logistic model for day t may be written as follows, with y=1 or 2.

$$\Pr(Y \geq y \mid Y(t-1), X) = \text{expit}(a(y) + X*\text{beta} + t*\text{tau}*[y=2] + \text{gamma}*[Y(t-1) = 1])$$

Here a(y) is the intercept corresponding to y, X represents baseline covariates, linear time effect, and a binary treatment indicator, beta are the main regression coefficients, and tau is a special effect of time t when y=2 (the partial PO effect). [z] denotes a 0-1 indicator function that is 1 if z is true, 0 otherwise.

A detailed case study using the proposed method, with code and results, may be found at https://hbiostat.org/rmsc/markov.html

The primary analysis will use R version 4.3.1 or later using the R VGAM package to fit the partial PO model and the Hmisc package to compute SOPs. Results will be displayed descriptively as 3-level stacked bar charts by treatment, covariate adjusted.

Likelihood ratio tests will be used for pivotal tests. These have better performance than Wald tests.

We do not expect missingness in our primary outcome. If there are missing covariates, cases will not be excluded; we will use multiple imputation with predictive mean matching for missingness in adjusting covariates.

Secondary and exploratory outcomes will also be modeled using the flexible family of generalized linear models with similar covariate adjustment. Statistically significant differences in secondary and exploratory outcomes will be calculated using either the Wilcoxon-Mann-Whitney non-parametric test for differences, the Chi-squared test, or Cox proportional hazards model with consideration given to the competing risk of mortality, whenever appropriate. Fidelity to obtaining nasal swabs, running the rapid PCR, and delivering results will be evaluated. The potential for differential treatment effects based on fidelity to the expected process of care may be explored.

There may be missingness in secondary or implementation outcomes. The cohort for which the outcome is available will be described, along with the results of the model evaluating treatment effects in this cohort. All model results will be summarized with point estimates and 95%

confidence intervals (CIs), which will be emphasized over p-values when reporting the results for secondary and implementation outcomes. No adjustments for multiplicity will be made.

Additionally, a descriptive analysis of missingness tendencies is warranted. For example, logistic regression to predict the probability of missingness of an outcome measurement with predictors that include baseline variables and other outcomes that are never missing.

Differential treatment effects
To determine whether effects of treatment on the primary endpoint depends on any of the baseline characteristics, we will test the interaction between the baseline characteristics and treatment effect. This is done by adding, one-at-a-time the potential interacting factors to the model detailed above. Our detailed strategy for assessing differential treatment effects may be found at https://hbiostat.org/bbr/ancova.html#modeling-differential-treatment-effect. The prespecified potential interacting factors are as follows, Elixhauser comorbidity index, immunocompromised/immunosuppressed status, baseline CKD, and severity of illness.

Summary
The results of this study will help to determine whether reporting the results of a negative rapid PCR back to the provider, via a pager alert, results in decreased vancomycin utilization for critically ill adults with community-acquired pneumonia when compared with usual care. The analysis approach described is selected based on the trial's pragmatic nature and the intent to understand the effectiveness of MRSA nasal swab PCR screening along with antimicrobial guidance in reducing inappropriate vancomycin usage in patients with community-acquired pneumonia.

Version and Revision Log

9/25/2023	Version 1: developed with and approved by Frank E Harrell, Jr., PhD.
2/8/2024	Version 2: Edits developed and approved by Frank E Harrell, Jr., PhD. Revisions: • Changing the study name.
1/22/2025	Version 3: Edits developed and approved by Frank E Harrell, Jr., PhD. Revisions: • Changing the study sample size • Correcting the logistic regression formula equation, page 8