Statistical Analysis Plan: Impact of a **Pro**calcitonin-guided Antibiotic Treatment Algorithm Plus Antibiotic Stewardship on Antibiotic Use in the **P**ediatric **I**ntensive **C**are **U**nit (ProPICU)

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INTRODUCTION

This is the Statistical Analysis Plan (SAP) for Impact of a **Pro**calcitonin-guided Antibiotic Treatment Algorithm Plus Antibiotic Stewardship on Antibiotic Use in the **P**ediatric **I**ntensive **C**are **U**nit (ProPICU). This SAP lays out the planned analyses for this study.

STUDY SCHEMA AND OBJECTIVES

DESIGN — Single-center, prospective, pre-assigned cluster multiple crossover trial to evaluate whether a procalcitonin (PCT) testing and treatment algorithm, implemented through daily antimicrobial stewardship audit and feedback, can promote early and safe antibiotic de-escalation in the pediatric intensive care unit.

DURATION — Duration of hospitalization or up to 30 days if they remain hospitalized.

SAMPLE SIZE — 280 unique participants

POPULATION — All patients admitted to the pediatric intensive care unit or pediatric cardiac intensive care unit started on IV antibiotics within 1 calendar day will be eligible.

NUMBER OF SITES — 1

STRATIFICATION — None

PRIMARY OBJECTIVE

The primary objective will be to evaluate the impact of a procalcitonin-guided antibiotic algorithm with antimicrobial stewardship guidance on overall antibiotic.

SECONDARY OBJECTIVES

Secondary objectives will be to evaluate the impact of a procalcitonin-guided antibiotic algorithm with antimicrobial stewardship guidance on broad-spectrum antibiotic use, and time to antibiotic modification.

CLINICAL/SAFETY OBJECTIVES

Clinical objectives will include 30-day mortality, length of intensive care unit stay, length of overall hospital stay, ventilator days, antibiotic-associated complications, infection with a multi-drug resistant algorithm, or hospital re-admission.

EXPLORATORY OBJECTIVES

Exploratory objectives will be to evaluate the impact of a procalcitonin-guided antibiotic algorithm with antimicrobial stewardship guidance on adherence to the procalcitonin-guided algorithm, impact of procalcitonin-guided algorithm on antibiotic stewardship recommendations, impact on antibiotic use in a subgroups of patients with a diagnosis of pneumonia, patients who have antibiotics initiated due to concern for sepsis, patients with initial procalcitonin levels <0.5 ng/mL versus those with initial procalcitonin levels >0.5 ng/mL, patients without comorbidities, and patients admitted to the pediatric intensive care unit vs. those admitted to the pediatric cardiac intensive care unit.

DEFINITIONS

1. **Antibiotic escalation:** Changing to a broader spectrum antibiotic, addition of one or more antibiotics, or conversion of oral (PO) to intravenous (IV) route.

2. **Antibiotic de-escalation:** Changing to a narrower spectrum antibiotic, cessation of one or more antibiotics, or changing from an IV to PO route of appropriate drug.

3. **Broad-spectrum antibiotic:** Vancomycin, daptomycin, amikacin, ceftazidime, cefepime, piperacillin/tazobactam, aztreonam, carbapenems

4. **Antibiotic-associated complications**: Defined as rash, neutropenia, thrombocytopenia, acute kidney injury [defined as increase in serum creatinine >0.3 mg per dL or >1.5-fold from baseline, or urine output <0.5 mL per kg per hour for more than six hours], hepatotoxicity [defined as >2-fold increase in alanine aminotransferase, ALT, or conjugated bilirubin], or *C. difficile* infection

5. **Multi-drug resistant organism:** Methicillin-resistant *S. aureus*, vancomycin-resistant *Enterococcus*, 3rd generation cephalosporin non-susceptible *Enterobacteriaceae*, multi-drug resistant *Pseudomonas aeruginosa* [resistant to aminoglycosides, cephalosporins, fluroquinolones, and carbapenems), carbapenem-resistant *Acinetobacter* and *Candida* spp. obtained from otherwise sterile sites [i.e. blood or urine cultures]

OUTCOME MEASURES

Primary Outcome Measures

1. Median days of therapy (DOT) per patient of antibiotic therapy (in days) within 14-days post randomization.

Secondary Outcome Measures

1. Median DOT per patient of broad-spectrum antibiotic therapy (in days) within 14-days post randomization.
2. Median time from randomization to first appropriate antibiotic escalation or de-escalation based on patient's clinical status and available supporting laboratory evidence, or lack thereof, of specific type of infection within 14-days post randomization.

Clinical Outcome Measures

1. In-hospital mortality within 30 days of randomization.
2. Length of stay in the hospital after randomization, up to 30 days, for those patients alive at 30 days. Length of stay will be date of discharge minus date of randomization.
3. Days in the ICU during hospitalization after randomization, up to 30 days, for those patients alive at 30 days.
4. Days spent using invasive ventilation methods (not including supplementary oxygen via nasal cannula or Vapotherm support) within 14-days post randomization.
5. Number of antibiotic-associated complications per patient within 14-days post randomization.
6. Acquisition of new hospital-acquired infections (HAIs) and/or multidrug resistant organisms (MDROs) within 30 days during index hospitalization identified on routine clinical or surveillance samples
7. Hospital re-admission within 30 days (yes/no)

Post Hoc Exploratory Analyses

1. Median DOT per patient of intravenous antibiotic therapy (in days) within 14-days post randomization
2. Antibiotic use > 72 hours (categorical) for any antibiotic, broad-spectrum antibiotics or IV antibiotics.
3. Count (%) of patients on 2 or more antibiotics at 24, 48, 72 and 96 hours after enrollment.
4. Total number of antibiotic stewardship recommendations made in each arm within 48-hours post randomization.

5. Rate of clinical provider compliance with adherence to suggested antibiotic escalation or de-escalation made by the antimicrobial stewardship team.
6. The primary endpoint will be analyzed comparing patients who:
    - Have antibiotics initiated due to concern for sepsis
    - Receive a clinical diagnosis of pneumonia
    - Have initial procalcitonin levels <0.5 ng/mL versus >0.5 ng/mL
    - Have no comorbidities versus those with comorbidities
    - Are in the pediatric intensive care unit at randomization
7. Number of antibiotic stewardship recommendations made in each arm within 48-hours post randomization will be analyzed (chi2 value will be compared between groups):
    - Male vs. female patients
    - Patients who receive a clinical diagnosis of pneumonia
    - Patients who have antibiotics initiated due to concern for sepsis
    - Patients who have initial procalcitonin levels <0.5 ng/mL versus >0.5 ng/mL

A. General Analysis Considerations

Data summaries and analyses will be presented by randomized arm.

To ensure participant confidentiality, listing of individual patient level data will be minimized as much as possible during study monitoring and for analyses. If such data are provided, they will be indexed with a unique blinded identifier or with identifiers removed. Study dates will not be presented, but provided as days/hours since randomization, as appropriate.

Participants who died prior to randomization, underwent bone marrow transplant or solid organ transplant prior to or after randomization, who are diagnosed with cystic fibrosis, or who ultimately are diagnosed with endocarditis, osteomyelitis, meningitis, mediastinitis or other invasive infection for which long duration of antibiotics is needed will be considered unevaluable for the primary outcome.

B. Statistical Monitoring Considerations

Routine statistical monitoring of accrual, study conduct, and data completion will be conducted by the statistical team and the study coordinator.

C. Monitoring Procalcitonin Algorithm Adherence

The study coordinator is responsible for monitoring intensive care unit provider adherence to the procalcitonin algorithm and, in the event of non-adherence, for soliciting reasons why they chose not to adhere to the algorithm.

D. Interim Analysis Considerations

The statistical team will perform an interim analysis when recruitment reaches 50% of goal accrual, to ensure safety of the procalcitonin-guided algorithm. Baseline characteristics such as age, sex and indication for antibiotics, primary outcome of overall DOT per patient within 14-days after randomization, and secondary outcomes of 30-day mortality and length of intensive care unit stay will be compared between groups.

E. Final Analysis Considerations

The primary analysis will be conducted when data from the last participant enrolled has been received.

The final analysis population will include participants who meet all eligibility criteria and no exclusion criteria.

The analysis will evaluate the primary, secondary, and exploratory outcomes in the procalcitonin-guided and control arms.

F. Analysis Plan

Statistical Considerations

Table summaries will present the following study population characteristics by randomized arm. All variables, as noted below, will be analyzed on the continuous scale or as categories or both as appropriate.

For continuous variables, summary statistics will include # of participants and median (Q1-Q3).

For categorical variables, summary statistics will include number (%) for each category. In calculation of percentages, participants with missing data will not be included in the denominator.

We will calculate the median days of antibiotic therapy per patient within the first 14-days post randomization in both treatment arms, together with the interquartile range. The primary test will be a Wilcoxon rank-sum test without the assumption of normality.

We will compare other continuous outcomes using a Wilcoxon rank-sum test, and categorical outcomes using a Pearson's chi-squared test.

We will perform a post-hoc analysis using a multivariable ordinal logistic regression model to assess the association between randomization group and the overall antibiotic duration of therapy per patient, adjusting for sex, recent surgical procedure, antibiotic indication of possible sepsis, and fever, vasopressor support and need for mechanical ventilation at enrollment.

We will perform a Cox proportional odds model adjusting for location of enrollment and study day to evaluate the hazard ratio for time to cessation of antibiotics within 4-days and within 10-days.

Final Analysis Considerations

The primary analysis will be a modified intention to treat (ITT) analysis. Participants who died prior to randomization, underwent bone marrow transplant or solid organ transplant prior to or after randomization, who are diagnosed with cystic fibrosis, or who ultimately are diagnosed with endocarditis, osteomyelitis, meningitis, mediastinitis or other invasive infection for which long duration of antibiotics is needed will be considered unevaluable. These are all issues that would otherwise qualify as exclusion criteria at the time of enrollment.

1. Study Population

1.1 Accrual

1. Figure (flowchart): Number of patients assessed for eligibility, number excluded and reasons for exclusion, number (%) who underwent randomization, number assigned to each group, number excluded from modified intention to treat analysis, number included in each arm for modified intention to treat analysis.

1.2 Study Population Characteristics

Table: Demographics

a. Current age on day of study entry (in years): Continuous
b. Sex at birth: By category (male/female)
c. Self-reported race, ethnicity and race/ethnicity as defined by NIH reporting standards: By category

2. Health Characteristics/Status at Entry

a. In pediatric ICU or pediatric cardiac ICU at randomization
b. Requirement for intravenous vasopressor agents (categorical, yes or no)
c. Mechanical ventilation (categorical, yes or no)
d. Fever (temperature >38.0 deg F) or hypothermia (temperature <35.0 deg F) (categorical, yes or no)
e. Surgical procedure within 2 weeks prior to enrollment (categorical, yes or no)
f. Presence of comorbidity
    - Heart disease
    - Gastrointestinal disease
    - Neurologic disease
    - Bone/joint infection
    - Renal disease
    - Hematologic disease
    - Oncologic disease
    - Pulmonary disease
    - Other
    - No comorbidities
g. Indication for antibiotics
    - Concern for sepsis
    - Pneumonia
    - Meningitis/encephalitis
    - Urinary tract infection
    - Other
h. Attending physician on the day of enrollment

- Choose 1 of 20 pediatric ICU attending physicians who wrote the progress note for the patient on the day of enrollment

3. Antibiotic Use

Table: Days of antibiotic therapy per patient within 14 days (PRIMARY OUTCOME). Patients who are continued on antibiotics longer than 14 days will be assigned a time of 14 days per antibiotic.

Table: Days of broad-spectrum antibiotic therapy per patient within 14 days. Patients who are continued on broad-spectrum antibiotics longer than 14 days will be assigned a time of 14 days per antibiotic.

Table: Count (%) of patients on any antibiotic longer than 72 hours

Table: Count (%) of patients on broad-spectrum antibiotics longer than 72 hours

Table: Count (%) of patients on IV antibiotics longer than 72 hours

Table: Count (%) of patients on 2 or more antibiotics at 24, 48, 72, and 96 hours after enrollment

Table: Days of IV antibiotic therapy per patient within 14 days. Patients who are continued on IV antibiotics longer than 14 days will be assigned a time of 14 days per antibiotic.

Figure: Time to first antibiotic modification, using the empirical cumulative distribution function.

Figure: Percent of patients on antibiotics within 14 days of enrollment, using a Cox proportional hazards model

4. Sensitivity and Additional Analyses of the Primary Endpoint

Table: Days of antibiotic therapy per patient within 14 days, restricted to patients with a final diagnosis of pneumonia.

Table: Days of antibiotic therapy per patient within 14 days, restricted to patients with sepsis as their indication for antibiotics.

Table: Days of antibiotic therapy per patient within 14 days, restricted to patients with an initial procalcitonin level < 0.5 ng/mL.

Table: Days of antibiotic therapy per patient within 14 days, restricted to patients with an initial procalcitonin level > 0.5 ng/mL.

5. Antimicrobial Stewardship

Table: Number (%) of patients with a stewardship recommendation made within 48-hours of enrollment

Table: Number (%) of stewardship recommendations accepted in each arm

Table: Number (%) of recommendations to de-escalate therapy

Table: Number (%) of recommendations to escalate therapy

Table: Number (%) of recommendations to optimize dose

Table: Number (%) of recommendations to consult the infectious diseases service

Table: Number (%) of recommendations to de-label a beta-lactam allergy

Table: Number (%) of recommendations that were not accepted due to provider discretion

Table: Number (%) of recommendations that were not accepted due a patient medication allergy

Table: Number (%) of recommendations that were not accepted due provider waiting for 48-hour culture results

Table: Number (%) of recommendations that were not accepted due to unknown reasons

Table: Number (%) of any antibiotic change that was initiated by pediatric intensive care provider, pediatric infectious diseases provider or stewardship provider

Table: Number (%) of antibiotic escalation that was initiated by pediatric intensive care provider, pediatric infectious diseases provider or stewardship provider

Table: Number (%) of antibiotic de-escalation that was initiated by pediatric intensive care provider, pediatric infectious diseases provider or stewardship provider

6. Clinical Outcomes

Table: Number (%) of death within 30 days of randomization
Median time from randomization to death among patients who died

Table: Median length of stay within 30 days after randomization

Table: Median length of ICU stay within 30 days after randomization

Table: Number (%) with antibiotic complication

Table: Number (%) with infection with multi-drug resistant organism

Table: Number (%) with hospital re-admission within 30 days

7. Sensitivity analysis

1. Demographics table including age, sex, race comparing those approached but not enrolled in the study.
2. Primary outcome analysis restricting to patients in the procalcitonin arm who had at least one procalcitonin level drawn.