Prospective, Randomized Controlled Trial to Evaluate the Impact of a Procalcitonin Testing and Treatment Algorithm on Antibiotic Use and Outcomes in the Pediatric Intensive Care Unit

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1.0 Background

The timely use of effective antibiotics can markedly reduce the morbidity and mortality associated with bacterial infections, particularly in the intensive care unit (ICU). However, in this setting, much antibiotic use is empiric, and administered to patients with non-bacterial or non-infectious causes of inflammation that do not respond to antibiotics. This widespread empiric use of antibiotics drives the emergence of multi-drug resistant organisms and antibiotic-associated adverse events, such as *C. difficile* infections. De-escalation of broad-spectrum empiric antibiotics for ICU patients without proven bacterial infections can reduce unnecessary antibiotic use, slow the development of antibiotic resistance, and reduce complications associated with antibiotic therapy. Thus, antibiotic de-escalation is an important goal of antimicrobial stewardship programs. Specific tests and pathways to predict which patients have bacterial infections and those that would benefit from antibiotic therapy would accelerate de-escalation and greatly facilitate antimicrobial stewardship efforts.

Procalcitonin (PCT) has been investigated as a biomarker for critically ill adult patients with bacterial infection, particularly pneumonia and sepsis. Following bacteria-induced activation of monocytes and adherence of monocytes to endothelial surfaces, procalcitonin is expressed and secreted. PCT levels have been shown to rise rapidly and remain elevated during ongoing bacterial infections, and PCT levels are more specific for bacterial infections than CRP or total white blood cell count. PCT rises approximately 4 hours after bacterial exposure, peaks between 12-24 hours, and has a half-life of 24 hours once the infectious stimulus is removed.

2.0 Rationale and Specific Aims

In many adult trials investigating PCT-guided algorithms for antibiotic cessation (refer to section 3.0), a high proportion of providers (up to 50%) chose not to follow algorithm guidance for subjects randomized to the PCT-guided group. *Thus, although PCT appears to be a useful guide for safe antibiotic de-escalation in the ICU, the ideal method for implementing the test and integrating it into clinical care in order to maximize its impact in the pediatric population is unclear.* Notably, none of the prior trials evaluated PCT-associated outcomes in critically ill children nor integrated PCT testing into antimicrobial stewardship activities.

PCT will be available for routine clinical care across all hospitals at VUMC in July 2017. To better understand the role of PCT in patient management, we will complete a pilot study prior to routine use of PCT in clinical care in the pediatric ICU. We propose the evaluation of a PCT testing and treatment algorithm on patient outcomes in the pediatric ICU, a setting in which PCT-guided antibiotic de-escalation has not been previously studied.

The proposed project will 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 ICU. We will conduct a pragmatic, prospective randomized controlled trial comparing antimicrobial use and outcomes among children admitted to the ICU who receive either: 1) Routine laboratory testing and treatment with antimicrobial stewardship review (control), or 2) PCT testing

and treatment with antimicrobial stewardship review (intervention). In both arms, baseline daily review of antimicrobial management by the stewardship team will occur. In the intervention arm, the stewardship provider (S.K.) also will recommend PCT testing and antibiotic modifications using a PCT-based treatment algorithm (Fig 1). *This research is not to determine if PCT is a good test; this has already been established and evaluated as part of the FDA approval process. This pragmatic outcomes trial is evaluating if use of the PCT, implemented together with antimicrobial stewardship program oversight, improves the quality of care we can provide for children at VCH.* We hypothesize that patients in the intervention arm will have shorter duration of antibiotic therapy and similar outcomes, as compared to patients in the control arm.

Specific Aims

1. **Compare antimicrobial utilization among children in the ICU who receive standard-of-care testing plus stewardship vs. PCT-based treatment plus stewardship.** We will compare days of antibiotic therapy in the first 14 days following randomization between the study arms. We will test the hypothesis that duration of antibiotic therapy will be 2 days shorter in the group with PCT-guided management vs. the group with standard of care testing and treatment.
2. **Compare clinical outcomes and safety among children in the ICU who receive standard-of-care testing plus stewardship vs. PCT-based treatment plus stewardship.** We will compare mortality, length of stay, recurrence of infection, and antibiotic-associated adverse events (rash, myelosuppression, renal impairment, hepatotoxicity, *C. difficile* infection) between the study arms. We will test the hypothesis that outcomes and safety will be comparable between the study arms.

3.0 Animal Studies and Previous Human Studies

Multiple studies have demonstrated that PCT-guided algorithms for antibiotic cessation result in significantly shorter antibiotic courses, with no increase in adverse clinical outcomes, in the treatment of pneumonia in adults and children, and in adults with sepsis. Based on these studies, the US FDA has recently expanded PCT indications to include its use to guide antibiotic management in adult patients with respiratory tract infections and/or sepsis. Baer *et al* (*PLoS One*, 2013) demonstrated that antibiotic courses could be safely and significantly shortened for pediatric patients with pneumonia from 6.3 days to 4.5 days under PCT guidance. Levels were measured on presentation and at days 3 and 5 of therapy with strict adherence to PCT level guidelines: discontinuation of antibiotics was encouraged upon clinical stabilization and when PCT values fell below 0.25 µg/L or, for patients with initial PCT values > 10 µg/L, when levels decreased below 90% of the initial value. In a recently published randomized, controlled, multi-center trial of 1575 adult ICU patients, de Jong *et. al* (*Lancet Infectious Diseases,* 2016) demonstrated that PCT-guided antibiotic treatment, with antibiotic de-escalation when PCT level fell to 80% of its peak value or to 0.5 µg/L or lower, could safely and significantly shorten antibiotic

duration from 7 days in the standard of care group to only 5 days in the PCT-guided group, without a significant difference in mortality rates.

4.0 Inclusion/Exclusion Criteria

Eligible subjects will be identified on admission to an intensive care setting by monitoring daily ICU census in EPIC.

Subjects will be enrolled if they:

- Are prescribed or administered antibiotics in the hospital within 1 calendar day of enrollment.
- Are admitted to the pediatric ICU (units 5A or 5C)
- Have parents or legal guardians who provide informed consent, or provide consent themselves if 18 years of age or older
- Provide assent if >7 years of age

Subjects will be excluded if they meet any of the following criteria:

- Are not prescribed antibiotics in the hospital
- Receive intravenous antibiotics within 7 days prior to identification for study enrollment
- Primary or secondary immune deficiency
- History of malignancy, bone marrow transplant or solid organ transplant
- A diagnosis of cystic fibrosis
- Neonates < 34 weeks gestation
- Patients receiving treatment for endocarditis, osteomyelitis, meningitis, mediastinitis, or other invasive infection, for which long durations of antibiotics are needed.
- Do not provide informed consent/assent

5.0 Enrollment/Randomization

The study will begin after PCT becomes available at VUMC, and after IRB approval. Enrollment will occur over 16 months.. Eligible subjects will be identified on admission to an intensive care setting by monitoring daily ICU census and a clinical pharmacy surveillance platform (Sentri7). Investigators will obtain consent (for all subjects) and assent (for subjects >7 years of age) by discussing the study with the patient and guardian in a private room, using the IRB-approved consent and assent forms. Privacy will be assured, Subjects will be permitted 24 hours to make a decision to participate. Investigators will assure that subjects comprehend the nature of the study by asking questions to assess their understanding of study objectives and procedures, and the risks and benefits of participation. All steps will be taken to avoid coercion. Subjects will be assured that if they decline to participate, they will continue to receive standard of care treatment in the PICU. Investigators will complete a combined consent-authorization document.

Enrolled subjects will receive either: 1) Standard of care testing and treatment with antimicrobial stewardship review (control), or 2) PCT testing and treatment with antimicrobial stewardship review (intervention).

6.0 Study Procedures

Study Design

The proposed study is a prospective randomized controlled trial among children admitted to the ICU setting at Vanderbilt Children's Hospital (VCH). Enrolled subjects will receive one of two management strategies: 1) Standard of care with antimicrobial stewardship review (control), or 2) PCT testing and treatment with antimicrobial stewardship review (intervention). All subjects in both arms will have baseline audit of antimicrobial orders with feedback to providers by the antimicrobial stewardship team. For subjects in the intervention arm, the stewardship team will additionally recommend PCT testing and treatment per algorithm (Fig 1). PCT will be used in conjunction with clinical status and exam, and results of radiographic and laboratory studies, to make medical decisions about antibiotic therapy. The PCT will never be used as the sole basis for making decisions to modify or stop antibiotic therapy. The antibiotic stewardship clinicians will review all enrolled subjects (in control and intervention arms) and provide recommendations regarding antimicrobial therapy.

The ultimate decision to obtain PCT testing and/or adhere to the PCT algorithm or stewardship recommendations will be at the discretion of the ICU attending physician. Preliminary discussions with ICU faculty have revealed that they are highly supportive of the proposed study, and would be willing to adhere to the study protocol.

Implementation of Antimicrobial Stewardship Directed PCT Testing and Treatment Algorithm

The antimicrobial stewardship team currently performs daily prospective audit and feedback for all patients admitted to VCH who receive antibiotics, providing in-person recommendations regarding antimicrobial modifications to providers as needed. This will continue in the standard of care arm. Current standard of care includes obtaining blood cultures, with or without CRP or other laboratory studies, and administering one or more broad spectrum antibiotics such as cefepime, piperacillin-tazobactam, and vancomycin for a minimum of 48 hours.

Prior to study initiation, the antimicrobial stewardship team will perform targeted education to ICU providers (attending physicians, residents and nurse practitioners) on the benefits and limitations of PCT use. A PCT-based algorithm to guide clinician decisions about antibiotic escalation or de-escalation will be disseminated to ICU providers (Fig. 1), displayed in ICU workrooms, and available on the intranet. PCT levels will be measured daily for the initial 3 days following randomization and then at day 5 post-randomization. Subjects in the intervention group will have a stewardship provider (S.K.) review their records daily and make in person rounds in the ICU to strongly encourage provider adherence to the PCT testing and algorithm-based management. De-escalation of antibiotics will be recommended if the PCT level falls by 80% or more of the peak PCT level, or when the PCT level is less than or equal to 0.25 μg/L (Fig. 1). Continuation or escalation of antibiotics will be recommended if PCT level is greater than or equal to 0.5 μg/L, or increased as compared to previous peak PCT level. These levels are comparable to those used in previously cited studies.

Laboratory Analysis

The Roche Procalcitonin test is a diagnostic test that is FDA approved for use in adults and has been approved by the VUMC laboratory formulary committee. It will be available

for routine clinical use across the medical center, including in children at VCH in the near future. Although the Roche PCT test is not approved for use in children, the same test manufactured by Biomerieux does not have an age restriction on its FDA approval. This study is not intended to support approval of the test in children, nor promote non-approved indications. In this study we will use the Roche PCT test in an off-label population (children), but it will be used within the scope of clinical practice at Vanderbilt, following VUMC-approved guidance. A group of ICU, ED, and ID physicians and the chemistry lab director were involved in developing the strategy for reporting PCT results in the VUMC electronic medical record. The planned test reporting comments and PCT threshold interpretations are more conservative than used in some studies (Fig. 1) and are shown below:

Procalcitonin can help differentiate viral from bacterial respiratory infection.
Procalcitonin may be used to guide antibiotic de-escalation in sepsis (when compared to admission level):

PCT < 0.1 ng/ml
Bacterial infection very unlikely

PCT 0.1 to 0.25 ng/ml
Bacterial infection unlikely

PCT 0.25 to 0.5 ng/ml
Bacterial infection possible

PCT > 0.5 ng/ml
Increased probability of bacterial infection, encourage antibiotic therapy

Serum PCT levels will be determined daily per VCH Laboratory protocol, using the Elecsys BRAHMS PCT test. The required blood volume is 0.5 - 1 mL and the estimated turn-around-time for the test is 3 hours or less. We will apply for a waiver of consent for the first blood sample, so that patients admitted to the ICU who are started on IV antibiotics will have leftover blood that is obtained during routine clinical care stored in a study refrigerator until study consent is obtained. For subjects enrolled in the intervention arm, PCT levels will be monitored at study enrollment, every 24 hours for the initial 2 days following randomization, and then at day 5 post-randomization. Whenever possible, leftover serum, from clinically collected specimens, will be used for PCT testing. For subjects in both arms, CRP, white blood cell count, and other relevant laboratory tests that are obtained for routine clinical care will be abstracted from the medical record.

Study Outcomes
The **primary outcome** is days of antibiotic therapy in the first 14 days following randomization. **Secondary outcomes** are duration of broad-spectrum antibiotic therapy (defined as vancomycin, daptomycin, amikacin, ceftazidime, cefepime, piperacillin/tazobactam, aztreonam, carbapenems), time from randomization to first appropriate antibiotic modification (escalation or de-escalation), 30-day mortality, re-initiation of antibiotics for a bacterial infection within 30-days of antibiotic discontinuation, length of ICU stay, length of overall hospital stay, ventilator days, rates of antibiotic-

associated complications (i.e. rash, neutropenia, thrombocytopenia, acute kidney injury [defined as increase in serum creatinine $\geq$ 0.3 mg per dL or $\geq$ 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), infection with multi-drug resistant organisms (defined as methicillin-resistant *S. aureus*, vancomycin-resistant *Enterococcus*, 3rd generation cephalosporin non-susceptible *Enterobacteriaceae*, multi-drug resistant *Pseudomonas aeruginosa* [resistant to aminoglycosides, cephalosporins, floroquinolones and carbepenems], carbepenem-resistant *Acinetobacter*, and *Candida* spp obtained from otherwise sterile sites [i.e. blood or urine cultures]), cost of antibiotics from hospital billing data, and adherence to the PCT-guided algorithm.

Study Timeline

The VUMC clinical laboratory PCT validation is complete. This protocol has been approved by the VUMC IRB. Provider education, and PCT clinical algorithm development is complete. We estimate that we will attain the target sample size within 16 months. Data analysis and abstract and manuscript preparation will be completed in the year after the study closes.

7.0 Risks

Risks include those associated with routine blood draws – pain, redness, soreness, bruising, or infection may occur at the needle stick site. Rarely some people faint. We plan to offer EMLA cream to subjects prior to blood draws. A maximum of 4 blood draws will be obtained for procalcitonin testing in patients randomized to the intervention arm. Whenever possible, for PCT testing, we will use leftover blood from routine laboratory testing performed as part of ICU care.

Because PCT has not been well studied for making antibiotic modification decisions in children, there may be the risk of premature cessation of antibiotics. However, to prevent this from happening, all decisions to stop or continue antibiotic therapy will be made by the ICU attending physician, based on clinical judgement and standard of care studies such as bacterial cultures, WBC,CRP, and radiographic evaluations

The decision to start antibiotic treatment will in no way be affected by the study. In all subjects antibiotics will be started based on clinical suspicion of infection or microbiologic evidence of infection. This decision is at the discretion of the treating intensive care physician. Similarly, the decision to obtain PCT testing and/or adhere to the PCT algorithm or stewardship recommendations will be at the discretion of the ICU attending physician.

All subjects in both arms will have baseline audit of antimicrobial orders with feedback to providers by the antimicrobial stewardship team. For subjects in the intervention arm, the stewardship team will additionally recommend PCT testing and treatment, with recommendations to initiate or expand antibiotic use at PCT levels > 0.5 ug/L and to stop antibiotics when PCT levels decrease by >80% from peak concentration or to an absolute value < 0.25 ug/L.

Multiple studies to date have demonstrated that procalcitonin-guided antibiotic de-escalation algorithms are as safe as standard of care management in the adult ICU setting. As such, we do not anticipate increased risk of infection relapse rates or

increase in 30-day mortality between groups. These parameters will be monitored throughout the study and adverse events will be recorded and reported as detailed below.

8.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Clinical adverse events will be monitored and recorded throughout the study. Serious adverse events include death, or other life-threatening complications like hemorrhage.Adverse drug/device events include if the PCT test result leads to premature cessation or de-escalation of antibiotics and causes harm to the patient, as determined by the PI or treating providers. Serious adverse device events include if PCT test results lead to premature antibiotic cessation, resulting in death, as determined by the PI or treating providers. All adverse events, adverse drug events, serious adverse events, and serious adverse drug events will be recorded by the study team in the RedCap data collection form and reported in an expedited manner to Roche, the VUMC IRB (in accordance with the Vanderbilt IRB Procedure III.L.1 – v.17.) and the FDA as required.

9.0 Study Withdrawal/Discontinuation

Subjects can withdraw from the study at any time.

10.0 Statistical Considerations

Based on data from studies evaluating PCT use among adult ICU patients, we estimate that median consumption of antibiotics will be 2.0 days less in the PCT group as compared to the control group.[7, 18] Assuming normal distribution, and a standard deviation of 6 days, a sample size of 125 patients per arm will provide at least 80% power to detect a difference in antibiotic duration of at least 2.0 days between study arms. These calculations are based on a chi-squared test with a two-sided Type 1 error rate of 0.05. Per clinical pharmacy data, the average duration of an antibiotic course per patient in VCH ICUs is 4 days, thus a difference of 2.0 days would be clinically significant.

11.0 Privacy/Confidentiality Issues

Data and specimens will be coded and protected according to institutional policies and protocol. Blood samples will be run on the day that they are obtained, and will only be stored afterwards according to routine laboratory protocol. Any blood that is obtained with routine clinical care on admission to the pediatric ICU but not used for the study will be discarded in an appropriate biohazard container within 24 hours of when it was drawn. Drs. Katz and Banerjee will maintain a password-protected master key with protected health information, and each patient case/medical record will have a unique identifier code and the master key will be the only link between the clinical records and the corresponding laboratory data. In addition, recorded patient identifiers (MRN, name, DOB) will be kept with the master key only. All other clinical data will be recorded in a

designated electronic data abstraction spreadsheet, which will be password-protected and separate from the patient identifiers and the key.

Vanderbilt, Dr Banerjee and her staff will comply with any and all laws regarding the privacy of protected health information.

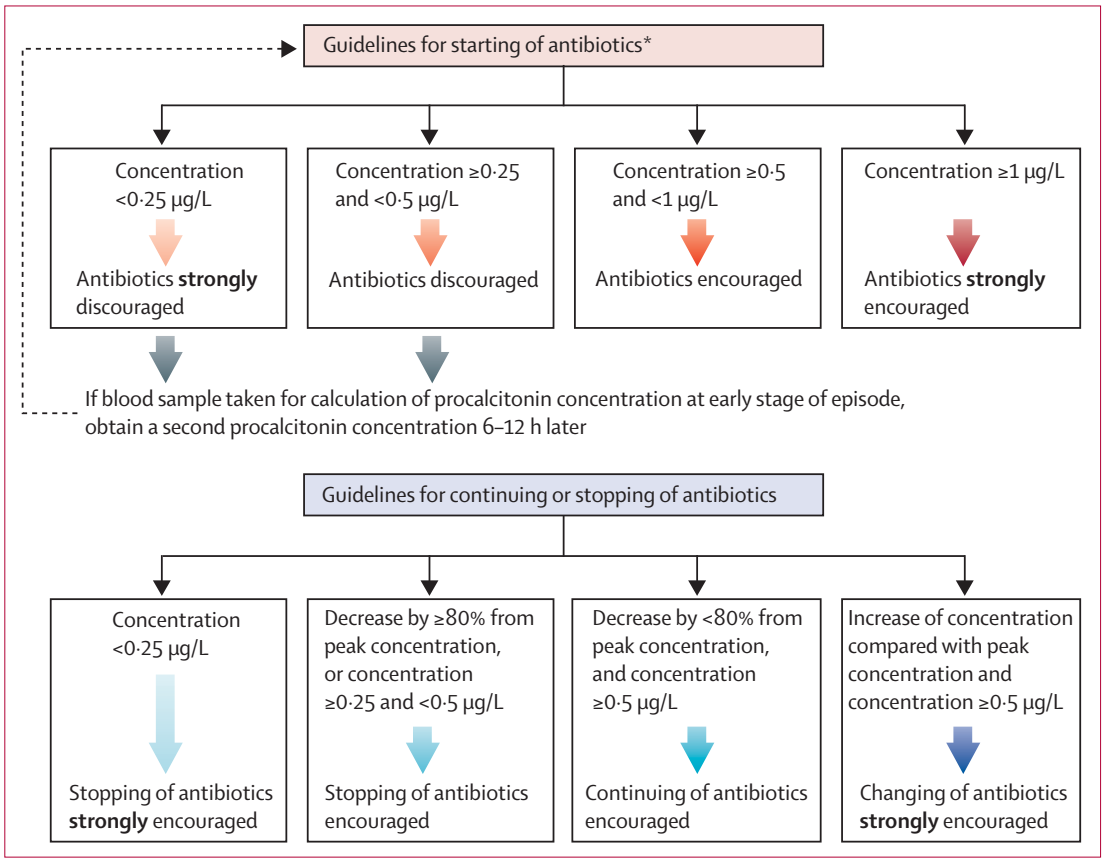
12.0 Follow-up and Record Retention

The projected duration of the study is from the time of IRB approval through June 30, 2019.

Data will be stored in a password-protected RedCap database. Paper copies of the data will be kept to the absolute minimum. Only the PI and co-investigators will have access to the master patient key and patient identifiers during the study collection period. After the collection period, only the PI will maintain the master patient key for future study that may require linking clinical laboratory values with clinical data. The key will be maintained in the PI's office in the Section of Infectious Diseases at VUMC on a single password-protected hospital computer. Any paper copies or data on paper will be stored in a locked filing cabinet in the PI's office. Paper copies will be destroyed at the earliest possible time by being discarded in the hospital HIPAA-approved receptacles for PHI to be shredded according to hospital policy.

The PI, co-investigators and laboratory personnel will be appropriately trained to maintain the confidentiality and protection of PHI according to the study design and hospital practice.

Appendix A: Figure 1 – Procalcitonin-Guided Algorithm



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