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CRC Research Course IRB Protocol:
Epidemiology of Health-Care Acquired Infections in Children Undergoing Cardiac Surgery

1. Study Purpose and Rationale

Post-operative infections can occur in children undergoing high-risk surgeries such as cardiac surgery for congenital or acquired heart disease. These hospital-acquired infections (HAIs) can increase morbidity and mortality, as well as health care costs, in these patients.[1] These infections include surgical site infections (SSIs), including both superficial and deep, as well as mediastinitis, a serious complication that has been shown to increase mortality and length of hospital stay.[2] The use of foreign bodies, including artificial valves, pericardial patches, and pacing wires, can be a risk factor for these infections. Additional HAIs include bloodstream infections (BSIs), both those associated with central lines (CLABSIs), and non central line-associated BSIs, ventilator-associated pneumonia (VAP), and urinary tract infections (UTIs), which can be associated with the use of indwelling urinary catheters.

It has been shown that perioperative antimicrobial prophylaxis can reduce rates of SSIs in pediatric patients.[3,4] However, inappropriately long courses of antimicrobial prophylaxis can result in adverse effects, increase rates of infection with resistant organisms in current patients or in those that follow, and increase health care costs.[5,6,7] These concerns emphasize the need for antimicrobial stewardship.

Outcomes are potentially complicated in a pediatric population as compared to adults by the relative immunocompromise of very young patients, prolonged surgeries for congenital cardiac disease, and possible differences in the pattern of causative microorganisms.[8,9] Specifically, causative organisms for SSIs in adult patients are dominated by those that are Gram-positive. It was been observed that children display a relative increase in infections caused by Gram-negative organisms. Noting a significant difference in the etiology of these infections could potentially lead to a change in prophylaxis recommendations, as current prophylaxis guidelines prioritize superior Gram-positive coverage.

NYP guidelines for the perioperative prophylaxis for cardiac surgery at NYP are in place,[10] and recommend the use of cefazolin 30 mg/kg/dose (up to 1-2 grams) IV q6-8h for 24 to 48 hours for the majority of patients. For β-lactam-allergic patients, clindamycin 10 mg/kg/dose (up to 900 mg) IV q8h or vancomycin 15 mg/kg/dose (up to 1 gram) IV q8h may be used, with clindamycin being preferred. Antibiotic should be initiated in the hour prior to incision time. The current guidelines allow for modifications of the regimen in patients with pre-existing infections, significant length of hospital stay prior to surgery, and/or history of positive cultures or colonization with resistant organisms, such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, or multi-drug resistant Gram-negative bacilli.

Based on prior observations, the guidelines that have been most vulnerable to non-adherence at Morgan Stanley Children's Hospital at New York-Presbyterian (MS-CHONY) are the timing of the start of antibiotics and the duration of treatment. In particular, antibiotics are at times started too early, likely as a result of a delay in incision time for a variety of factors, some of which are patient-related and unavoidable. Also, it is known that antibiotics are frequently continued past the first 24 to 48 hours in cases where there is an indwelling foreign body, such as a thoracostomy or mediastinal tube, although this is against the current guidelines. However, current practices in antimicrobial prophylaxis in infants and children undergoing cardiac surgeries and the subsequent impact on HAIs and other outcomes have not been systematically assessed.

2. Study Design and Statistical Procedures

Aim I: Assess perioperative antimicrobial prophylaxis prescribing practices for children 18 years of age or younger undergoing cardiac surgery at MS-CHONY, and receiving their post-operative care in the pediatric cardiac intensive care unit (PCICU), from January 2011 through December 2012. We will measure adherence to current recommendations, including antibiotic choice, dose, timing, intraoperative re-dosing (if applicable), and length of treatment.

Aim II: Assess the epidemiology of HAIs among children 18 years of age or younger undergoing cardiac surgery, and determine rates of specific infections, including central line-associated bloodstream infections (CLABSIs), non-CLABSI bacteremia, early post-operative endocarditis, SSIs, VAP, and UTI in the post-operative period, from day of surgery until initial hospital discharge.

Aim III: Assess the antimicrobial susceptibility of pathogens associated with the HAIs.

Aim IV: Determine the effect of receiving appropriate prophylaxis on the length of hospital stay. There are numerous confounders that can be predicted to affect hospital stay. For example, a patient who is on ECMO for an extended period of time will have a prolonged hospital stay and is also at risk for receiving inappropriately long antimicrobial prophylaxis. Due to this anticipated complication of this observational study, we will use propensity analysis and perform multiple logistic regression (see below for details).

Study Design:
This study is a cohort study of children 18 years of age or younger undergoing cardiac surgery and hospitalized in our PCICU and/or cardiac unit CHONY 6-Tower. Data from January 1, 2011 to July 31, 2011 will be collected retrospectively, and data from August 1, 2011 through December 31, 2012 will be collected prospectively.

Case determination of surgical site infections (SSI) categorized as superficial, deep tissue, or organ space, e.g., mediastinitis; endocarditis; CLABSIs; non-CLABSI bacteremia; VAP; and UTI will be made by the study team in collaboration with the Department of Infection Prevention & Control using CDC/NHSN case definitions.[11]

Plausible risk factors for receiving inappropriate antimicrobial prophylaxis to be investigated will include:

Demographic characteristics: age, sex, race, ethnicity, prematurity.

Comorbid conditions: e.g., asthma, chronic lung disease, cystic fibrosis, diabetes mellitus, neuromuscular conditions, sickle cell disease, cancer history, chronic immunosuppression, chronic renal disease, or chronic cardiac disease.[12]

Surgical procedure(s)-related: complexity and length of cardiac surgery; open chest procedures; use of extracorporeal membrane oxygenation (ECMO); cardiopulmonary bypass time; aortic cross-clamp time; use of deep hypothermic circulatory arrest; volatile blood glucose levels; delayed sternal closure; repeat surgical intervention.

Foreign bodies and devices: thoracostomy tubes, mediastinal tubes, and pacing wires; use of mechanical ventilation, central venous catheters, and urinary catheters.

Medications/Infusions: antibiotics, corticosteroids, parenteral nutrition/ intralipids, blood transfusions.

Other: history of prior infections or colonization with resistant organisms, pre-operative hospitalization, previous stay in a chronic care facility.

Statistical Procedures:

1. We will measure the rates of adherence to antibacterial prophylaxis guidelines.
2. We will measure rates of the HAIs listed above.
3. We will characterize the organisms and antimicrobial susceptibility of the HAIs, and compare with current prophylaxis guidelines.
4. By analyzing the probable risk factors for patients NOT receiving the appropriate antimicrobial prophylaxis, we will determine a propensity score for each patient to receive the appropriate antimicrobial prophylaxis. We will not consider the patients with extremely low or extremely high propensity scores. For example, a patient who has a short admission for an ASD repair, and reliably and predictably receives prophylaxis according to the guidelines, or a patient who receives ECMO for one week, for whom prophylaxis continues until the cannulas are removed, will not be considered. We will then perform a multiple logistic regression, pairing children with the same propensity scores who do and do not receive appropriate prophylaxis, and determine the effect of appropriate prophylaxis on length of hospital stay.

   If the average length of hospital stay ranges from about 4–10 days, the standard deviation is approximately 1.5 days. Twelve hours, or 0.5 days, is a clinically and economically significant amount of time to observe between the two groups. Using an unpaired t-test for 80% power, testing at P=0.05, we will need 150 patients in each group. By starting with approximately 700 patients, we anticipate having more than enough patients, even following the above propensity analysis where a number of patients will be excluded.

3. Study Procedures

This study will review existing data only. All data will be obtained as a part of routine patient care. No data will be obtained solely for the purposes of this study.

Data obtained from the electronic medical record (Eclipsys XA, Webcis, MicroEpi, Compurecord) will include: culture results (blood, wound, sputum, urine, and prior infections, if applicable); serum and urine antigen testing; fevers; hypothermia; white blood cell count; oxygen requirement; radiographic findings; echocardiography results; urinalysis; duration of open chest cavity; use of devices and foreign bodies; autopsy and histopathological data (if available); antibiotic type, dosage, interval, and duration; incision time; length of surgery; cardiopulmonary bypass time; length of PCICU/hospital stay; drug allergies.

4. Study Drugs or Devices

Not applicable.

5. Study Instruments
Not applicable.

6. Study Subjects
All children 18 years of age or younger at the time of their surgery, and hospitalized in the PCICU at MS-CHONY for their post-operative care will be included in this study. Eligibility for inclusion will be determined from the hospital admission database, PCICU admission database, cardiac surgical database, and OR manager database.

From trends in prior years, we estimate there will be approximately 350 children undergoing cardiac surgery each year who are eligible for inclusion, for a total of ~700 patients in this study. Children hospitalized in the PCICU who do not undergo cardiac surgery, or children undergoing cardiac surgery who are not hospitalized in the PCICU, will be excluded from this study.

7. Recruitment
This is an observational study only. There will be no active intervention. Therefore, patients will not be recruited for this study.

8. Informed Consent Process
We request a waiver of documentation of informed consent, as this is an observational study in which only existing data will be reviewed. No data will be collected solely for the purposes of this study, and no active intervention will be performed. In addition, the epidemiologic nature of the study precludes limiting it to only patients that consent, as it may introduce significant bias.

9. Confidentiality of Study Data
Data will be maintained on the password-protected computers of the investigators at CUMC. Subjects will be given a unique study identification number for data analysis purposes. The link between this identification number and subject identifiers will be destroyed at the end of the study, after all data have been cleaned and results have been published.

10. Privacy Protections
A unique study identification code will be assigned to all subjects for data analysis. Identifying data will not be published or presented at committee meetings or scientific meetings. Identifying data will only be made available to study personnel, the IRB, and Federal oversight agencies as needed.

11. Potential Risks
This only risk of this study is the potential loss of confidentiality. This risk will be minimized by assigning a unique patient identifier and limiting access to the patient identifiers, as described above in "Confidentiality of Study Data" and "Privacy Protection."

12. Data and Safety Monitoring
Not applicable, as this is an observational study only with no active intervention.

13. Potential Benefits
Determining current practices in antimicrobial prophylaxis can help determine barriers to adherence to guidelines, and serve as a benchmark to track improvement. Recognizing patterns of infection and resistance, as well as risk factors for HAIs, can help to tailor future interventions for prevention of HAIs in children undergoing cardiac surgery.

14. Alternatives
Not applicable.

15. Research at External Sites
Not applicable.

16. Columbia as Lead Institution
Not applicable.

References

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