Rapid Blood Culture Identification Panel in Pediatric Patients in Guatemala

NCT05314816

Study Protocol

v. 4/4/2022

Guatemala BCID2 Study Protocol- COMIRB Protocol Approved

Project Title: Clinical impact of a multiplex PCR blood culture identification panel in early identification of positive blood cultures in pediatric patients in Guatemala

I. **Hypotheses and Specific Aims**:

1. Primary Aim: The primary aim of this study is to assess the clinical impact of a rapid multiplex PCR blood culture identification panel on time to optimal antimicrobial therapy when compared to conventional microbiological culture methods in children hospitalized in a low resource setting in Guatemala City.
2. Secondary aims:
    a. To assess the impact of the blood culture identification panel on reduction in time to organism identification when compared to conventional microbiological culture methods
    b. To assess the impact of the blood culture identification panel on time to effective antimicrobial therapy, mortality, length of stay, and ICU days.
3. We hypothesize that we will see an overall reduction in time to optimal antimicrobial therapy following implementation of the panel.

II. **Background and Significance**: There are high rates of blood culture positivity and antimicrobial resistance in Latin American countries, with high rates of broad-spectrum antimicrobial utilization[1-3]. Based on our preliminary analysis of pediatric blood cultures at Hospital Roosevelt, the rates of carbapenem-resistant Klebsiella and Acinetobacter are 65% and 90%, respectively. Because of this, patients are often started empirically on broad-spectrum antibiotics until the organism and susceptibility results are identified. Rapid microbiology diagnostics, such as the Biofire Film Array BCID, have been shown to greatly impact clinical care in high-income countries[4,5]. The best strategies for implementation and their potential clinical impact in low-middle income countries, however, have not been well defined. Hospital Roosevelt in Guatemala City is a 900-bed public hospital with 180 beds dedicated to pediatric patients. It serves 53% of children in the larger metropolitan area of Guatemala. Co-investigator has a long-standing relationship with Hospital Roosevelt and has partnered with Hospital Roosevelt on previous research studies. PI has an active research study at Hospital Roosevelt involving rapid diagnostics for Pneumococcal disease.

We have just completed a program evaluation to evaluate the current rates of positive blood cultures, time to pathogen identification, and time to effective and optimal antimicrobial therapy at Hospital Roosevelt Pediatric Department. Based on preliminary data, Hospital Roosevelt has an average of 800 pediatric blood cultures per month, with 5% positivity (roughly 45 positive pediatric blood cultures per month)[6]. The laboratory relies primarily on standard culture techniques for organism identification, which takes a median of 78 hours[7]. With the implementation of a blood culture identification panel (BCID2), we expect to reduce the time to organism identification significantly, and therefore reduce time to optimal antimicrobial therapy. In order to facilitate this, we will couple the BCID2 results with antimicrobial stewardship that is already in place. Based on U.S. data conducted at our institution, implementation of Biofire Film Array BCID showed a reduction in time to optimal antimicrobial therapy to 27 hours on average with BCID plus antimicrobial stewardship.[5]

III. **Preliminary Studies/Progress Report:**

We have just completed a program evaluation at Hospital Roosevelt Pediatric Department in Guatemala City. We have retrospectively reviewed 99 consecutive available patient charts with positive blood cultures, and have analyzed current time to organism identification, time to effective and optimal antimicrobial therapy, as well as mortality rate. These will serve as historical controls. The current median time to pathogen identification is 78 hours with a range

of 34-122 hours[7]. Only 37% of patients achieved optimal therapy; of those the median time to optimal therapy was 90 hours[7]. Mortality rate among this cohort was 20%[7].

IV. Research Methods

A. Outcome Measure(s):

Primary Outcome:

1. Time to optimal antimicrobial therapy from the time of specimen receipt in the laboratory

Secondary Outcomes:

1. Time to pathogen identification from the time of specimen receipt
2. Time to effective antimicrobial therapy from the time of specimen receipt
3. Length of hospital stay
4. Mortality
5. Total antibiotic days (number of antibiotics per day X number of days)
6. Total ICU days

Exploratory outcomes:

1. Cost analysis
    a. Grams of antibiotics used
    b. Days of hospitalization
    c. ICU days

B. Description of Population to be Enrolled:

a. Pediatric patients birth to 18 years of age
b. Patients on all pediatric and neonatal inpatient units at Roosevelt Hospital
c. First positive blood cultures on admission or during hospitalization

C. Study Design and Research Methods

a. Currently the standard of care at Hospital Roosevelt is to perform standard blood culture on all specimens that are positive on the automated VIRTUO system. This occurs by trained lab technicians 24/7. Once there is colony growth on the plates via standard culture, the isolate is placed on the VITEK system for identification and susceptibility. This process has been analyzed in the program evaluation and will serve as historical controls.
b. In this prospective study, we will implement the BioFire FilmArray blood culture identification panel (BCID2), which laboratory technicians will run simultaneously with standard culture after it flags positive on VIRTUO system. We will only run the BCID2 panel on those specimens that become positive during **normal working hours Monday-Friday from 7am to 1pm** due to the inability to staff the laboratory overnight and on weekends. **Those specimens that become positive from 12am to 7am will be run at 7am, as the panel can be run up to 24 hours from positivity per BioFire protocol.** Those that become positive in the evening from 1pm-11:59pm Monday-Thursday will not be run on the BCID2 and will serve as controls. All positive cultures (in both groups) will be plated on agar plates to confirm growth on culture and undergo susceptibility testing per standard current protocols.
c. Physicians will be notified of panel results, as well as standard culture results per current laboratory protocol, which includes uploading results onto a webpage accessible to all physicians on their mobile device. **BCID2 results will additionally be reported to providers directly by telephone notification or in person by the study PI**. Standard culture results on control patients will be reported per standard protocol of webpage notification.
d. Antimicrobial stewardship will be continued per current standard of care at Hospital Roosevelt. The Pediatric Infectious Disease fellows and attendings at Hospital Roosevelt review all positive cultures in the microbiology laboratory each morning,

and review results in person with the inpatient teams. **During this study, the local PI will serve as the antimicrobial steward and provide BCID2 results to physicians within 1 hour of notification. We will provide guideline-based recommendations for all BCID2 results to help standardize the stewardship process.**

e. We will compare time to optimal antimicrobial therapy (primary outcome), as well as secondary outcome measures, between the intervention group and the 2 control groups (historical controls, as well as concurrent controls).

D. Description, Risks and Justification of Procedures and Data Collection Tools: The panel will be performed all on positive pediatric blood cultures that are positive during laboratory working hours. The panel results will be released to clinical providers. This is necessary in order to assess the clinical impact and clinical decision-making based on the results. A local investigator will review all positives throughout the day and inform the treatment team of the results. All enrolled patients will undergo chart review to assess for clinical outcomes, such as antimicrobial agents, ICU days, hospital days, and mortality. We will need to collect this information in order to assess the clinical impact of this panel. The information will be stored directly into RedCap database which will be accessible only to key study personnel. The study involves minimal risk to the patient, as it only includes risk of loss of confidentiality. We are requesting a full waiver of informed consent, as subjects will be assigned to the intervention versus control group based on the timing of positive cultures. Patients, providers and investigators will not have control over which patients will be placed into the control or intervention groups, as this will be randomized based on time of positivity. This reflects the reality of laboratory capabilities in low-middle income countries, such as Guatemala.

E. Potential Scientific Problems: There will be challenges of working in Guatemala City, as this is a limited-resource setting. The culture around antibiotic usage is different than in the U.S. and therefore may impact the expected reduction in time to effective and optimal antimicrobial therapy. Currently they only obtain a single blood culture bottle during collection, but this is standard in many low-middle income countries.

F. Data Analysis Plan: Hospital Roosevelt has 800 pediatric blood cultures processed monthly (with about 5% positivity)[6]. Based on preliminary data, only 37% of patients with positive blood cultures received optimal therapy based on predefined consensus guidelines. Of those who receive optimal therapy, the median time to therapy is 90 hours[7]. With the addition of a blood culture identification panel, we expect to see a reduction in time to optimal antimicrobial therapy to 30 hours. This estimate is based on U.S. data conducted at our institution showing a reduction to 27 hours on average with BCID plus antimicrobial stewardship.[5]

Target Enrollment: 100 patients over 4 month study period

G. Summarize Knowledge to be Gained: This study is important to evaluate the impact that rapid multiplex blood culture identification PCR panels have on improving clinical outcomes in low-middle income countries such as Guatemala. It has shown significant impact in reduction in time to optimal antimicrobial therapy in high-income countries. In countries such as Guatemala, with higher rates of antimicrobial resistance and broad-spectrum antimicrobial usage, the potential impact is greater and could lead to a mortality benefit. If a significant clinical impact is observed, we would advocate for continued use of the panel at Hospital Roosevelt, as well as 24/7 implementation if a significant difference is seen between the intervention and prospective control group. This could be translatable to other low-middle income countries.

H. References:

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4. Messacar K, Hamilton SL, Prinzi AM, et al. Rapid identification of nonblood sterile site broth cultures using the FilmArray blood culture identification panel. *Diagn Microbiol Infect Dis.* 2019;93(1):22-23.
5. Messacar K, Hurst AL, Child J, et al. Clinical Impact and Provider Acceptability of Real-Time Antimicrobial Stewardship Decision Support for Rapid Diagnostics in Children With Positive Blood Culture Results. *Journal of the Pediatric Infectious Diseases Society.* 2017;6(3):267-274.
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