Statistical Analysis Plan

Implement and PREDICT Shock:
An Implementation Trial of Predictive Modeling to Enhance Diagnosis and Improve Critical Treatment in Pediatric Septic Shock

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1. Introduction

Septic shock is a leading global cause of pediatric death. In the US, the in-hospital mortality rate for children with sepsis is 5-20%.[1, 2] Septic shock is a state of critical infection that requires advanced and resource-intensive resuscitation, and morbidity-free survival depends on timely diagnosis. Critical care delivered in a delayed fashion, after a child is in hypotensive shock, is less effective; for each hour of unrecognized shock the odds of death more than double.[3] Advances have been made in timely sepsis treatment, but improving diagnosis of septic shock in children remains elusive. Improved early diagnosis would accelerate treatment and improve outcomes.

Tools that have been deployed to improve diagnosis in pediatric sepsis either diagnose it after organ dysfunction criteria have been met, or depend heavily on subspecialty physician judgment and have not been tested outside of tertiary pediatric hospitals.[4, 5] Thus, the evidence-based 2020 Surviving Sepsis Children's Guidelines for pediatric sepsis stated that "high-quality trials on pediatric sepsis recognition are lacking, and data are not sufficient to suggest any particular screening tool," and identified pediatric sepsis recognition trials as an important research need.[6] Despite this, the guidelines weakly recommended screening patients "who present as acutely unwell" for septic shock, citing very low quality evidence. The guidelines also stated that there is no evidence for the effectiveness of any existing pediatric sepsis screening tools.

This study addresses a gap in knowledge about the effectiveness of pediatric sepsis prediction tools. The study team has developed and retrospectively validated early diagnostic models that leverage clinical data in the Electronic Health Record (EHR) to predict septic shock in children in the emergency setting.[7, 8] In order to address concerns about alert fatigue and antibiotic overuse, these predictive models were designed to identify patients at high risk for shock among patients in whom clinicians initially had some suspicion for sepsis.

2. Study design

This study is a prospective, stepped-wedge cluster randomized trial to test the effectiveness of implementing a Clinical Decision Support (CDS) tool for prediction of septic shock in four Emergency Departments (ED) within a pediatric healthcare network. The site will be the unit of randomization. All ED providers at the site will receive the CDS intervention when their site receives the intervention. The outcomes will be measured at the patient level. There will be five, 10-week study periods and four sites. In the first period, no sites will receive the intervention. During each subsequent period, one site will crossover to receive the intervention.

2.1 Sample size calculation

The unit of analysis for this study is ED patients with suspected sepsis. The necessary enrollment size was used to calculate the study period necessary to achieve power, based on historic volume trends. The main calculations were done using the pwr[9] package for R.

During the study period, we expect 2054 patients to be identified and exposed to decision support (CDS). With current care patterns, we would expect 25% (514) to receive guideline-

concordant septic shock care prior to shock occurring.[10] In the literature, use of pediatric sepsis quality interventions has increased rates of concordant early care of shock to 50% (1027).[11-13] With an estimated effect of the alert of increasing rates of concordant care from 25% to 50%, using a significance of 0.05, we anticipate >90% power to detect this difference. We will have 80% power to detect an increase of 6%.

For the outcome of time to receipt of antibiotic, we expect that 79% of patients will receive antibiotics. Among those who do receive antibiotics, with current care patterns, in pilot data we have observed a mean time to antibiotics of 55 minutes, or a mean log time of 4.0 (SD 1.29). In published pediatric sepsis literature, the use of pediatric sepsis quality interventions has decreased the log time to antibiotic to 3.3 (SD 1.54).[11-14] Using a significance of 0.05, we anticipate >90% power to detect a difference in this outcome.[15] We have 80% power to detect a smaller difference of 4.0 vs 3.8 (55 to 45 minutes). Even under conditions of very slow accrual where half of the hypothesised sample is realized, we would have 80% power to detect a difference of 4.0 vs 3.72 (55 to 41 minutes).

Minimal necessary sample size to fit the multivariable models

For the binary outcome of guideline-concordant care, the model for sensitivity analyses will have up to 9 degrees of freedom (intercept + 3 (4 sites) + 4 (five time periods) + 1 for treatment). Using the rule of tens, we must have at least 90 outcomes. In the worst case scenario, there will be no treatment effect and 25% of the sample should have the outcome. This yields a minimal needed sample of 90/0.25 = 360. In a univariable test, assuming a minimal detectable difference of 0.25, The power attainable would be 99.9%.

In the event that the treatment and control groups are imbalanced for some covariates, and 5 parameters are added, approximately 140 outcomes will be necessary to fit the model adequately. Then the minimal sample size becomes: 140/0.25 = 560. In a univariable test, assuming a minimal detectable difference of 0.25, The power attainable would be >99.9% under the expected sample size of 2054.

3. Aims and objectives

The objective of this trial is to test whether implementing a CDS tool for prediction of septic shock in four Emergency Departments within the Children's Hospital Colorado network increases the proportion of children with suspected sepsis who receive guideline-concordant septic shock care, decreases the time to antibiotics, decreases the proportion of patients with septic shock, decreases the proportion of patients who experience mortality within 30 days of hospital arrival. An additional objective is to assess the balancing measure of whether the proportion of patients with suspected sepsis who receive intravenous antibiotics increases.

4. Outcomes

4.1 Primary outcome

Number of Patients Receiving Guideline-Concordant Septic Shock Care

Treatment will be defined as concordant with Surviving Sepsis Campaign guidelines for shock if intravenous antibiotics are initiated within 60 minutes of sepsis recognition and an intravenous fluid bolus is initiated within 60 minutes of sepsis recognition. This will be a binary outcome. Sepsis recognition is defined as the earlier of: sepsis page sent, sepsis orderset use, or intravenous antibiotic order.
[Time Frame: Up to 24 hours after Emergency Department arrival]

4.2 Secondary outcomes

Time to Antibiotics
Time to antibiotics will be measured in minutes from the time of sepsis recognition to the start of intravenous antibiotic treatment. This will be a time-to-event outcome. Sepsis recognition is defined as the earlier of: sepsis page sent, sepsis orderset use, or intravenous antibiotic order.
[Time Frame: Up to 24 hours after Emergency Department arrival]

Number of Patients With Septic Shock
Septic shock will be defined as suspected infection and systolic hypotension and either vasoactive use or ≥30 ml/kg intravenous bolus fluid administration
[Time Frame: Up to 24 hours after Emergency Department arrival]

30-Day In-Hospital Mortality
The number of patients who experience an in-hospital death up to 30 days after Emergency Department arrival.
[Time Frame: 30 days after Emergency Department arrival]

Number of Patients Receiving Intravenous Antibiotics during Emergency Department care
[Time Frame: Up to 24 hours after Emergency Department arrival]

Other hospital course and resource utilization outcomes
Organ dysfunction laboratories measured
Sepsis orderset used
Arrival to Antibiotic Administration
ED Disposition
24-Hour hypotension
Intravenous crystalloid fluid volume administered/kg in the first 24 hours
Vasoactive agent used during hospitalization
Positive pressure ventilation during hospitalization
Hospital Length of Stay
ICU within 24 hours
ICU Length of Stay
Proportion of all ED patients triggering the CDS

4.3 Safety outcomes
Adverse events will be identified upon occurrence and on data review at the DSMC interim safety review and end of the study period.

5. Populations and subgroups to be analyzed

5.1 Subgroups

The primary analysis will be conducted in all patients meeting inclusion criteria. A subgroup analysis for the same outcomes will be conducted only in the subgroup of patients identified as high-risk by either the arrival or two-hour models. Assuming sufficient sample size, we will perform subgroup analyses in race/ethnicity groups, to assess whether the intervention differentially impacts socially constructed subgroups.

6. Analyses

The primary hypothesis will test whether the proportion of patients receiving guideline-concordant septic shock care is greater in the intervention arm compared to the control arm. An odds ratio will be calculated to assess this, and will be considered significant if the 95% confidence interval does not contain 1.0.

Analyses will be conducted at the level of the patient encounter using the generalized linear model framework. The primary analysis will include an effect for intervention, and subsequent sensitivity analyses will include fixed effects for time and site to test for heterogeneity of effect. Up to five additional covariates will be included if they are imbalanced between the two arms of the trial. We will construct tables comparing the medians and proportions of clinically meaningful variables that might be expected to affect the association between the intervention and the outcome of guideline-concordant care. These potential covariates considered will include patient characteristics, provider type, arrival modality, triage level, and social determinants of health, including race, ethnicity, and insurance status. Standardized differences will be used to assess the magnitude of difference in covariates between arms. Anywhere that we find significant imbalance between arms, that variable will be included as a covariate.

Significance of effects will be assessed at the 5% level, with all tests structured as two sided hypotheses. SAS software version 9.4 (SAS Institute, Cary, NC) and R version 4 (R Foundation for Statistical Computing, Vienna, Austria) will be used for all data management and statistical analysis.

6.2 Secondary outcomes (continuous – time to antibiotic)

The secondary hypothesis will test whether the time to antibiotics is shorter in the intervention arm compared to the control arm. A hazard ratio will be calculated to assess this, and considered significant if the 95% confidence interval does not contain 1.0. The following approach will be used.

Time will be measured beginning with admission to the ED and concluding with administration of antibiotics (an event) or discharge from the ED (censoring). Death is expected to be rare and will be treated as a censoring event. Analysis will use a Cox proportional hazard model with a fixed binary effect for treatment.

7. Missing data

Missing data are not expected in this dataset, which only includes existing clinical data on patients through hospital discharge or 30 days, whichever happens first.

8. References

1. Tan B, Wong JJ, Sultana R, et al. Global Case-Fatality Rates in Pediatric Severe Sepsis and Septic Shock: A Systematic Review and Meta-analysis. *JAMA pediatrics*. 2019;173(4):352-362.
2. Weiss SL, Balamuth F, Hensley J, et al. The Epidemiology of Hospital Death Following Pediatric Severe Sepsis: When, Why, and How Children With Sepsis Die. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies*. 2017.
3. Evans IVR, Phillips GS, Alpern ER, et al. Association Between the New York Sepsis Care Mandate and In-Hospital Mortality for Pediatric Sepsis. *JAMA : the journal of the American Medical Association*. 2018;320(4):358-367.
4. Eisenberg MA, Freiman E, Capraro A, et al. Outcomes of Patients with Sepsis in a Pediatric Emergency Department after Automated Sepsis Screening. *J Pediatr*. 2021;235:239-245 e234.
5. Balamuth F, Alpern ER, Abaddessa MK, et al. Improving Recognition of Pediatric Severe Sepsis in the Emergency Department: Contributions of a Vital Sign-Based Electronic Alert and Bedside Clinician Identification. *Annals of emergency medicine*. 2017.
6. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies*. 2020;21(2):e52-e106.
7. Scott HF, Colborn KL, Sevick CJ, et al. Development and Validation of a Model to Predict Pediatric Septic Shock Using Data Known 2 Hours After Hospital Arrival. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies*. 2021;22(1):16-26.
8. Scott HF, Colborn KL, Sevick CJ, et al. Development and Validation of a Predictive Model of the Risk of Pediatric Septic Shock Using Data Known at the Time of Hospital Arrival. *J Pediatr*. 2020;217:145-151 e146.
9. Champely S. pwr: Basic Functions for Power Analysis. R package version 13-0. https://CRAN.R-project.org/package=pwr. Published 2020.
10. Greenwald E, Olds E, Leonard J, et al. Pediatric Sepsis in Community Emergency Care Settings: Guideline Concordance and Outcomes. *Pediatric emergency care*. 2021;37(12):e1571-e1577.
11. Paul R, Melendez E, Stack A, et al. Improving adherence to PALS septic shock guidelines. *Pediatrics*. 2014;133(5):e1358-1366.

12. Larsen GY, Mecham N, Greenberg R. An emergency department septic shock protocol and care guideline for children initiated at triage. *Pediatrics*. 2011;127(6):e1585-1592.
13. Cruz AT, Perry AM, Williams EA, et al. Implementation of goal-directed therapy for children with suspected sepsis in the emergency department. *Pediatrics*. 2011;127(3):e758-766.
14. Paul R, Melendez E, Wathen B, et al. A Quality Improvement Collaborative for Pediatric Sepsis: Lessons Learned. *Pediatr Qual Saf*. 2018;3(1):e051.
15. Lakens D. Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. *Front Psychol*. 2013;4:863.