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A Neonatal Sequential Organ Failure Assessment (nSOFA) Score Predicts Mortality and Morbidity to Early- and Late-Onset Sepsis in Neonates

Abbreviated Title: nSOFA score for predicting mortality in neonates

A. Study Purpose and Rationale:

In neonates, bacterial sepsis is a major cause of morbidity and mortality, representing the 5th most common cause of neonatal death in term and preterm neonates combined[3]. Sepsis is subdivided into two categories in neonates, early-onset sepsis (EOS), beginning prior to 72 hours of life, and late-onset sepsis (LOS), beginning later than 72 hours of life. This distinction is made due to differences in infectious acquisition between EOS and LOS. EOS is largely attributable to vertical transmission, with Group B Streptococcus (GBS) and *E. Coli* representing approximately 75% of cases[7.] Common morbidities of EOS include neurodevelopmental handicaps chronic lung disease, hearing loss and seizures[4]. In contrast, LOS is acquired postnatally and is a leading cause of mortality in the neonatal intensive care unit[6].

While the issues associated with both early- and late-onset sepsis are clear, defining objective criteria for sepsis in neonates has been challenging. In adults and older pediatric patients, the Sequential Organ Failure Assessment (SOFA) score enables physicians to quantify life-threatening organ dysfunction. The absolute SOFA score, as well as the change in SOFA score over time, has been shown to correlate with ICU admission and mortality[1,5]. However, the SOFA Score is not applicable to neonates, in part because the clinical variables used to derive the SOFA score are not developmentally appropriate. In order to derive a similar operationalization method in assessing neonates with sepsis, the neonatal SOFA (nSOFA) was developed[9]. To date, the nSOFA has been studied in neonates with late-onset sepsis. Similar to adults, it has been shown that both the absolute nSOFA and change in nSOFA have associations with neonatal mortality risk[2]. However, it has yet to be shown whether the nSOFA score is applicable to neonates with early-onset sepsis and whether the nSOFA can help to predict either morbidity or mortality in this population of infants. A validated nSOFA score for early-onset sepsis would provide a basis for stratifying neonates for therapeutic interventions and antibiotic stewardship.

Aims

- Assess the utility of the nSOFA score in predicting morbidity and mortality outcomes in neonates with EOS
- Compare the traditional nSOFA score with the modified nSOFA score in predicting morbidity and mortality in neonates with EOS
- Provide further substantiation of the nSOFA score as an objective framework for defining and identifying sepsis in neonates

B. Study Design:

There are two arms to this study, an early-onset study arm and a late-onset study arm. The late-onset study arm is complete. My project focuses on the early-onset study arm.

This is a retrospective, single-center study of neonates admitted to one Level IV neonatal intensive care unit between 2013-2020. Neonates with early-onset (< 72 hours of life) infection as defined by bacteremia, or fungemia will be included in this study.

The aim of the early-onset study arm is to optimize and validate an nSOFA score for infants with early-onset sepsis. nSOFA scores will be derived using the traditional and a modified nSOFA scoring rubrics (defined below, Figures 1 and 2) in order to optimize a scoring system for the EOS population. In prior studies, it has been shown that both the absolute nSOFA and change in nSOFA scores derived from the traditional nSOFA scoring rubric have associations with late-onset sepsis-associated mortality risk[2]. However, it has yet to be shown whether the nSOFA score is applicable to neonates with early-onset sepsis and whether the nSOFA can help to predict either morbidity or mortality in the EOS population of infants. Variations of the nSOFA scoring rubrics will be compared in order to determine the optimal scoring system with which to predict morbidity and mortality in this population.

Outcomes and Measures

The primary outcome will be mortality associated with early-onset infection. The traditional and modified nSOFA scores from survivors and non-survivors with early-onset infection will be compared. Secondary outcomes include incidence of respiratory (bronchopulmonary dysplasia, respiratory support or oxygen requirement after 36 weeks post menstrual age), neurologic (intaventricular hemorrhage, periventricular leukomalacia), ophthalmologic (retinopathy of prematurity), and gastrointestinal (nerotrizing enterocolitis, spontaneous bacterial peritonitis) morbidities in neonates with early-onset infection.

Figure 1

Traditional nSOFA Score

Respiratory Score	0 Not intubated or intubated SpO2/FiO2 > 300	2 Intubated SpO2/FiO2 < 300	4 Intubated SpO2/FiO2 < 200	6 Intubated SpO2/FiO2 <150	8 Intubated SpO2/FiO2 <100
Cardiovascular Score	0 No inotropes No systemic steroids	1 No inotropes With systemic steroids	2 1 inotrope No systemic steroids	3 2 or more inotropes or 1 inotrope and systemic steroids	4 2 or more inotropes and systemic steroids
Hematologic Score	0 Platelet count > or equal to 150K	1 Platelet count 100K – 149K	2 Platelet count < 100K	3 Platelet count < 50K	

Figure 2: Modified nSOFA Score

Respiratory Score	1 Non-invasive ventilation FiO2 < or equal to 0.6 OR Respiratory Severity Score (RSS): MAPxFiO2 OR Oxygenation Index (OI): MAP x FiO2 x 100/PaO2 OR Oxygen Saturation Index (OSI): MAPxFiO2 x 100/SpO2	2 Non-invasive ventilation FiO2 > 0.6	4 Intubated (CMV) FiO2 < or equal to 0.6	6 Intubated (CMV) FiO2 > 0.6	8 High frequency ventilation or nitric oxide with CMV
Cardio-vascular Score	0 No inotropes or need for volume resuscitation OR Vasoactive-inotropic Score (VIS): dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 x epinephrine dose (μg/kg/min) + 10 x milrinone dose (μg/kg/min) + 10 x vasopressin dose (mU/kg/min) + 100 x norepinephrine dose (μg/kg/min)	1 No inotropes with need for volume resuscitation < 20ml/kg	2 No inotropes with need for volume resuscitation > 20ml/kg	3 Need for 1 inotrope	4 ECMO or need for 2 inotropes
Hematologic Score	0 Platelet count > or equal to 150K	1 Platelet count 100K – 149K	2 Platelet count < 100K	3 Platelet count < 50K	

Data to be Collected

- Outcomes
  - Mortality
  - Morbidity:
    - Respiratory (BPD, respiratory support or oxygen requirement after 36wks post menstrual age) For preterm infants. we will also look at respiratory support at 36 weeks gestation and classify infant according to the criteria of Jensen
    - Neurologic (periventricular leukomalacia or any grade intraventricular hemorrhage)
    - Ophthalmologic (Any ROP or Stage III ROP or higher)
    - GI (Necrotizing enterocolitis – Bell's Stage II or higher, SBP/SIP)

- Neonatal Demographics
  - Gestational age
  - Birth weight
  - 1 and 5-minute APGAR scores
  - Mode of delivery
  - Sex
  - Multiple gestations
  - Length of Stay
- Maternal Clinical Information
  - Maternal age
  - Antenatal steroids
  - Antenatal antibiotics (GBS specific or broad spectrum)
  - Intrapartum fever
  - Diagnosis of intraamniotic infection (ACOG criteria)
  - Duration rupture of membranes

    - GBS status
- Neonatal Clinical Information
    - Respiratory support settings
        - Type of support (intubation status, CPAP, NC)
        - Ventilator settings (at 6 and 24 hours)
            - Ventilator mode
            - Mean airway pressure (MAP)
            - PEEP
            - PIP
            - Respiratory rate (RR)
            - FiO_2
    - SPO2 (at 6 and 24 hours)
    - PaO_2 (at 6 and 24 hours)
    - Duration of mechanical ventilation
    - Duration of non-invasive ventilation
    - Base Deficit (most severe value)
    - Platelet count (first CBC)
    - Medications (including systemic steroids, Nitric oxide, and vasoactive-inotropic medications: dopamine, dobutamine, epinephrine, milrinone, vasopressin and norepinephrine)
    - Cardiovascular support (ECMO status, inotropes, systemic steroids, need for volume resuscitation)
    - Time of blood culture (HOL)
    - Blood culture pathogen isolated
    - CSF pathogen isolated
    - Time of antibiotic initiation (HOL)
    - Duration of antibiotic therapy
    - Cause of death
    - Time of death (HOL)
- Exclusion criteria
    - Positive blood culture for coagulase negative staphylococcus or other common contaminants
    - Chromosomal abnormality
    - Congenital abnormality
    - Outborn infants

C. Study Selection: All preterm and term infants admitted to the New York Presbyterian Columbia University Medical Center (NICU) between January 2013 through December 2020 who were diagnosed with early-onset (< 72 hours of life) infection will be included in this study. Early-onset sepsis is defined as event that meets all of the following criteria before data is extracted to reduce potential bias: 1) The event occurred before the end of the 3rd day of life, 2) subjective clinician concern for serious infection (demonstrated by a blood culture being performed, empiric antimicrobial treatment started at evaluation and continued for at least 7 days or until death), and 3) a single bacterial/fungal pathogen isolated from blood. Neonates with coagulase-negative Staphylococcus isolates, chromosomal or congenital abnormalities, and outborn infants will not be included.

D. Statistical Procedures: Continuous variables will be summarized as a median with quartiles (25 and 75th percentiles). Categorical variables will be summarized using percentages. Fisher

exact tests will be used for categorical variables and the Wilcoxon signed-rank test or Mann-Whitney for continuous variables. Areas under the receiver operating characteristic curves (AUCs) will be calculated.

E. Study Procedures: No procedures will be performed in this study.

F. Study Drugs: No study drugs, approved or investigational, will be given in this study

G. Medical Device: No medical devices will be used in this study.

H. Study Questionnaires: No study questionnaires will be utilized in this study.

I. Recruitment of Subjects: This study uses archived databases and no active recruitment will be performed.

J. Confidentiality: All possible attempts to ensure confidentiality of data will be made.

K. Potential Conflict of Interest: None of the investigators have any conflicts of interest to report.

L. Location of Study: The study will take place in the Morgan Stanley Children's Hospital neonatal intensive care units (9N, 7T, 8I) and the transitional nursery (10T).

M. Potential Risks: The research involves no more than minimal risk of loss of confidentiality, as the study is a chart review.

N. Potential Benefits: There are no potential direct benefits to the participants in the study, but benefits to advancing the scientific knowledge of neonatal early- and late-onset sepsis could be great.

O. Alternative Therapies: There will be no experimental therapies employed in this study.

P. Compensation to Subjects: No compensation will be provided to the study subjects.

Q. Costs to Subjects: The patients will not incur additional costs as a result of participating in this study.

R. Minors as Research Subjects: Data will be collected retrospectively from the electronic medical record on infants. Numerous precautions will be taken to protect the data.

S. Radiation or Radioactive Subjects: This study will not employ radiation or radioactive substances.

References

1. de Grooth HJ, Geenen IL, Girbes AR, Vincent JL, Parienti JJ, Oudemans-van Straaten HM. SOFA and mortality endpoints in randomized controlled trials: a systematic review and meta-regression analysis. Crit Care. 2017 Feb 24;21(1):38. doi: 10.1186/s13054-017-1609-1. PMID: 28231816; PMCID: PMC5324238.

2. Fleiss N, Coggins SA, Lewis AN, Zeigler A, Cooksey KE, Walker LA, Husain AN, de Jong BS, Wallman-Stokes A, Alrifai MW, Visser DH, Good M, Sullivan B, Polin RA, Martin CR, Wynn JL. Evaluation of the Neonatal Sequential Organ Failure Assessment and Mortality Risk in Preterm Infants With Late-Onset Infection. JAMA Netw Open. 2021 Feb 1;4(2):e2036518. doi: 10.1001/jamanetworkopen.2020.36518. PMID: 33538825; PMCID: PMC7862993.
3. Heron M. Deaths: Leading Causes for 2017. Natl Vital Stat Rep. 2019 Jun;68(6):1-77. PMID: 32501203.
4. Schrag SJ, Farley MM, Petit S, Reingold A, Weston EJ, Pondo T, Hudson Jain J, Lynfield R. Epidemiology of Invasive Early-Onset Neonatal Sepsis, 2005 to 2014. Pediatrics. 2016 Dec;138(6):e20162013. doi: 10.1542/peds.2016-2013. PMID: 27940705.
5. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):801-10. doi: 10.1001/jama.2016.0287. PMID: 26903338; PMCID: PMC4968574.
6. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics. 2002 Aug;110(2 Pt 1):285–91.
7. Stoll BJ, Hansen NI, Sánchez PJ, Faix RG, Poindexter BB, Van Meurs KP, Bizzarro MJ, Goldberg RN, Frantz ID 3rd, Hale EC, Shankaran S, Kennedy K, Carlo WA, Watterberg KL, Bell EF, Walsh MC, Schibler K, Laptook AR, Shane AL, Schrag SJ, Das A, Higgins RD; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. Pediatrics. 2011 May;127(5):817-26. doi: 10.1542/peds.2010-2217. Epub 2011 Apr 25. Erratum in: Pediatrics. 2011 Aug;128(2):390. PMID: 21518717; PMCID: PMC3081183.
8. Wynn JL, Kelly MS, Benjamin DK, et al. 2017 Timing of Multiorgan Dysfunction among Hospitalized Infants with Fatal Fulminant Sepsis. Am J Perinatol 34:633-639.
9. Wynn JL, Polin RA. A neonatal sequential organ failure assessment score predicts mortality to late-onset sepsis in preterm very low birth weight infants. Pediatr Res. 2020 Jul;88(1):85-90. doi: 10.1038/s41390-019-0517-2. Epub 2019 Aug 8. PMID: 31394566; PMCID: PMC7007331.