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Vital signs analysis algorithm detects inflammatory response in premature infants with late onset sepsis and necrotizing enterocolitis☆

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ABSTRACT

Background: Nonspecific clinical signs and suboptimal diagnostic tests limit accurate identification of late onset sepsis (LOS) and necrotizing enterocolitis (NEC) in premature infants, resulting in significant morbidity and antibiotic overuse. An infant's systemic inflammatory response may be identified earlier than clinical suspicion through analysis of multiple vital signs by a computerized algorithm (RALIS).

Aim: To evaluate the revised RALIS algorithm for detection of LOS and NEC in preterm infants.

Methods: In this nested case–control study, VS data (heart rate, respiratory rate, temperature, desaturations, bradycardias) were extracted from medical records of infants 23–32 weeks gestation. RALIS generated an output, with score ≥ 5 triggering an alert. Patient episodes were classified based on culture, radiograph, and antibiotic data into categories: LOS, expanded LOS, NEC, and controls. Paired t-tests, linear regression and cross-validation analyses were used to evaluate the relationship between RALIS alert and LOS/NEC.

Results: Among 155 infants with 161 episodes, there were 41 expanded LOS (+blood, CSF, urine, respiratory culture), 31 LOS (+blood, CSF, urine), 9 NEC, and 93 controls. RALIS alert was 43.1 ± 79 h before culture in LOS ($p = .012$). There was a significant association between RALIS alert and LOS/NEC ($\beta = 0.72$, $p < .0001$). Sensitivity and specificity for LOS/NEC were 84% and 80%, (PPV = 63%; NPV = 93%). The regression model demonstrated an AUC of 89.9%.

Conclusions: For infants ≤32 weeks, RALIS detects systemic inflammatory responses in LOS and NEC in the first month of life. The algorithm can identify infection earlier than clinical suspicion, even for NEC with negative cultures. RALIS has high NPV to rule-out LOS and NEC, and may, after prospective validation, aid in antibiotic treatment decisions.

1. Introduction

Sepsis remains a critical issue and a major cause of death among infants in the U.S [1]. and causes over 200,000 annual neonatal deaths worldwide [2]. Approximately 21% of very low birth weight (VLBW) infants are affected by at least one episode of late onset sepsis (LOS; with positive blood culture after 72 h of life) [3]. There has been some improvement in the incidence of LOS due to infection control measures [4], but LOS continues to disproportionately affect preterm infants and cause significant morbidities including neurologic impairment, prolonged hospitalization, and death [5]. Because prompt recognition of infection and initiation of antibiotic therapy decrease sepsis-related morbidity and mortality, clinicians have a low threshold to evaluate for LOS and empirically treat with broad spectrum antibiotics. However, the lack of reliable diagnostic capability for LOS remains an ongoing issue in the neonatal intensive care unit (NICU). Clinical signs of sepsis are mostly nonspecific and detected late, and current laboratory tools are of limited utility. Specifically, the current gold standard for diagnosis of LOS is blood culture, which has delayed results and limited sensitivity in the setting of small specimen volumes and recent antibiotic administration [6]. Adjunct markers of infection such as white blood cell count indices [7], C-reactive protein [8], hypoglycemia, and

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thrombocytopenia are also nonspecific with poor positive predictive value (PPV) [9, 10]. Furthermore, there is lack of consensus on the definition of neonatal sepsis among providers [11]. As a result, antibiotic treatment is overprescribed in the NICU with 56% of VLBW infants treated with antibiotics while only 21% had culture-proven infection in one large study [3]. The adverse effects of prolonged antibiotic exposure in preterm infants include antibiotic resistance, fungal infections, necrotizing enterocolitis (NEC), and death [12–14]. The nonspecific clinical presentation of NEC overlaps with that of sepsis. The early localized bowel inflammation, bacterial penetration, and tissue destruction is often difficult to identify until signs of abdominal distension, bloody stool, bowel perforation, or clinical deterioration appear, often accompanied by sepsis [15]. Thus, development of more reliable and specific methods to predict and exclude LOS and/or NEC in preterm infants is essential to improve neonatal outcomes.

The advantage of automated vital signs monitoring as an objective tool to detect evolving sepsis is being increasingly recognized [16–18]. Several studies have suggested that analysis of vital signs patterns can help clinicians evaluate for impending infection or inflammatory response (e.g., sepsis, NEC) prior to obvious deterioration [19–22]. For example, the HeRO monitoring system detects heart rate variability characteristics that change with LOS. The use of HeRO was associated with a reduction in 30 day mortality in VLBW infants [23, 24]. The RALIS software was the first to incorporate multiple vital signs monitoring into a predictive algorithm to detect systemic inflammatory responses including LOS [25, 26]. As we previously reported, RALIS detected sepsis 2.5 days prior to clinician suspicion of infection (defined as the time blood culture was obtained) with a sensitivity of 82% for LOS in infants ≤28 weeks gestational age (GA) [20]. However, the PPV and negative predictive value (NPV) were only 67% and 65% respectively. The RALIS algorithm was changed, primarily by incorporating more appropriate ranges for temperature and more accurate input of skin temperature rather than incubator values. The objective of the current study was to evaluate the performance of the revised RALIS algorithm to detect inflammatory responses from LOS and NEC in a cohort of preterm infants (23–32 weeks GA). Specifically, we compared time and frequency of RALIS alert to clinical suspicion of LOS among preterm infants with culture-confirmed LOS, NEC, and controls. Cross validation analysis was also performed to assess the robustness of the RALIS model.

2. Materials and methods

2.1. Patient population

Medical records of infants enrolled in a premature birth cohort study at Prentice Women's Hospital and who were admitted to the NICU were reviewed. Per standard study protocol, parental consent is obtained, patients are assigned a study code, and a de-identified database is stored on a secure server. Included infants were born at < 33 weeks GA between 2008 and 2012 with complete VS data from birth to 28 days of life available in the electronic medical record. In this study of diagnostic utility, infants transferred out of the NICU, who died early within the first month of life, and those with congenital syndromes were excluded. Infants requiring oscillator or jet ventilation were also excluded because of inability to accurately interpret respiratory rates. Maternal and infant characteristics including demographics and clinical course were collected using the cohort database, Northwestern University Enterprise Data Warehouse system, and standardized medical record review. Extracted data included comprehensive microbiologic culture information, type and duration of antibiotics, and laboratory results. This study was approved by the Institutional Review Board of Northwestern University and Ann and Robert H. Lurie Children's Hospital of Chicago.

2.2. Vital signs and RALIS output

Vital signs (VS) data are entered into the electronic medical record (PowerChart, Cerner, MO) by experienced nurses per routine NICU protocol. Nurses read the VS from the standard continuous cardiorespiratory monitors (IntelliVue Neonatal, Philips, MA), verify values clinically, and input values into the Powerchart record. All patients had vital signs documented at least every 3 h for 28 days of hospital admission. The VS data was extracted retrospectively, coded in Excel, and uploaded into the RALIS program in order to generate continuous RALIS output.

RALIS is a mathematical algorithm developed for monitoring of preterm infants to detect inflammatory response, such as in LOS. As previously described, the algorithm was originally developed from a derivation cohort of 200 infants at Bikur Holim Hospital, Jerusalem, Israel [26]. The software generates a RALIS score based on significant VS changes from the individual patient's baseline, which is initially calibrated from the first 72 h of life and evolves over the monitoring period. Additionally there are GA and birth weight specific VS ranges incorporated into the algorithm. VS data incorporated into RALIS include: heart rate, respiratory rate, temperature, desaturation events, and bradycardia events [20]. The heart rate, respiratory rate, and temperature values are numerical, while the low SpO2 (oxygen saturation) and bradycardic inputs are binary, indicating the presence or absence of events during the preceding 2–3 h interval. Nurses record the lowest oxygen saturation and heart rate during an episode and the duration (seconds) in the electronic medical record. For RALIS coding, a desaturation event was defined as an oxygen saturation of < 80% for > 10 s. A bradycardia event was defined as a heart rate < 100 beats per minute for > 10 s. Weight is entered once every 24 h. Each VS has a weighted contribution to the final algorithm output. There is a real-time current monitoring period, which the program uses to calculate significant aberrations from the baseline period, both of which are changing over time. The final RALIS score is reported on a 0–10 scale, with 5 as the threshold for an acute inflammatory response based on the initial derivation cohort in Israel. A RALIS score ≥ 5 for 6 consecutive hours generates an alert to the clinical team. We limited our analysis to LOS and NEC episodes within 3–28 days of life for consistency and comparison with previous studies [20, 26]. A RALIS alert was considered associated with a LOS or NEC episode if it occurred within 7 days before or after infection was suspected. The absence of any alert within 7 days before or after culture was considered false negative result for a LOS or NEC episode. A false positive alert in control infants was any signal throughout the 28-day monitoring period.

2.3. LOS definitions

The primary outcome: LOS was defined as an episode (physician-initiated sepsis evaluation) occurring at > 72 h of life which resulted in a positive culture and was treated with an antibiotic treatment course. A positive culture was defined as any blood, cerebrospinal fluid (CSF), or urine culture with bacteria or yeast. We also collected data on episodes with a positive endotracheal tube culture (ETT) and chest radiograph infiltrate treated with antibiotics: which were included in the *expanded* LOS classification. Antibiotic treatment was receipt of a ≥ 7 day of antibiotic course. Neonatal complications such as NEC [27] and bronchopulmonary dysplasia (BPD) [28] were identified according to parent study protocol and widely used benchmarks. Specifically, an episode of NEC was defined as clinical and radiographic evidence of NEC (pneumatosis intestinalis) treated with antibiotics and bowel rest. Based on NICHD definitions for premature infants, episodes of culture-proven sepsis occurring < 72 h of life were considered early onset and excluded from analysis. Patients with no positive culture and no antibiotic course throughout their hospitalization served as controls. Clinical sepsis patient episodes with negative culture, but that received