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COMMENT

Early recognition of neonatal sepsis using a bioinformatic vital sign monitoring tool

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Newborn infants are at risk for sepsis, particularly when premature,[1] and sepsis remains a leading cause of morbidity and mortality, especially among extremely preterm infants.[2] Early recognition and timely treatment of infection in high-risk infants in the newborn intensive care unit (NICU) can drastically improve outcomes and save lives. However, in the setting of clinical uncertainty and incomplete information, neonatologists must balance the risks of unnecessary antibiotic use and failing to treat unidentified (but present) infections. In fact, Horbar and co-workers show that, compared with uninfected matched controls, very preterm infants with early-onset sepsis died at higher rates and that survivors had significantly higher morbidity, highlighting the need for novel approaches to improve early detection of sepsis.[3] While the debate about criteria and timing for empiric antibiotics in infants with possible sepsis continues, it is imperative for clinicians to thoughtfully consider a patterned change in vital signs, in addition to more traditional assessments of change in clinical status and laboratory test abnormalities. Early identification of abnormalities in physiology that reveal "pre-failure" compensatory changes in homeostatic control of breathing, circulation, body temperature, and distribution of oxygen to tissues can prompt clinicians to act before infants demonstrate overt decompensatory physiology (e.g., shock, respiratory failure, etc.).

In the article, "Vital signs as physiomarkers of neonatal sepsis" by Sullivan and Fairchild,[4] the authors have reviewed "signature" patterned pathophysiologic changes in heart rate, respiration, and oxygen saturation (SpO_2) that occur with neonatal sepsis. The authors make a strong argument to integrate and utilize highly advanced real-time bioengineering/computational tools that read and incorporate the routine bedside vital signs into machine learning models. The advanced analytics and the predictive algorithm that is derived from continuous vital sign monitoring data can further assist clinicians with early recognition of sepsis, especially in intensive care units (ICUs).

So, what is the importance of this review and why does this matter to a bedside clinician in the NICU? Lifesaving and practice-changing innovations such as predictive algorithms extracted from bedside vital sign monitoring data can serve as a very powerful practice that can transform bedside decision-making in the setting of uncertainty and potentially improve outcomes for vulnerable infants in the NICU.

PRACTICE-CHANGING INNOVATION

The shift in focus from traditional interpretations of the physiologic events that occur after exposure to bacterial endotoxin or viral infection to an early pre-clinical exposure detection of the derangement in the intensity and dynamics of the physiologic cues associated with pathology is not new. Heart rate variability (HRV) is an established method for quantifying intrinsic parasympathetic–sympathetic "poise" of the autonomic nervous system (ANS), to reveal stress in homeostatic compensation as means to recognize "pre-failure" physiologic states.[5] Fetal HRV, a reflection of the ANS activity, is a useful marker for fetal well-being.[6] An absent fetal HRV signals severe fetal distress.[7] HRV analysis has been used in the prediction of cardiovascular and cerebrovascular events in adults, and sudden cardiac death.[8,9] Studies of HRV in normal sleeping full-term and preterm neonates, aged 31–41 weeks post-menstrual age (PMA) suggest a steep increase in vagal tone at 37–38 weeks PMA, with subsequent stabilization[10] and a more regular increase in sympathetic tone from 31 to 41 weeks PMA was observed. More recently, several studies have focused on recognizable patterns in autonomic dysregulation that occur in early sepsis.[9,11,12] Bloch et al. demonstrate a high level of predictive accuracy of sepsis detection with a high receiver-operating curve (0.88) based on bedside monitoring data in the adult ICU.[13] Sophisticated bioinformatics tools such as the HeRO (Heart Rate Observation) monitoring in newborn infants are associated with all-cause mortality reduction by 22% and sepsis-associated mortality by 40%[14], thereafter demonstrating robust clinical utility in the NICU. More recently, Joshi et al.[15] demonstrate infant motion besides HRV and respiration as a prognostic predictor for late-onset sepsis. Using the Naïve Bayes algorithm, pathologic heart rate decelerations, increased respiratory instability, and a decrease in spontaneous infant activity (lethargy) in the hours leading up to the clinical suspicion of sepsis was determined to have a higher prognostic potential for predicting late-onset sepsis. The underlying basis by which the pattern of HRV in early sepsis differs from that in (aseptic) hypoxia–ischemia remains unclear, but possible unique features of hypoxia–ischemia without infection may include (a) direct brainstem injury, (b) hypoxia-induced cardiac dysfunction that dysregulates the heart rate at the nodal level, or (3) systemic inflammatory response triggering adrenergic and cholinergic desensitization.[16]

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Table 1. Iatrogenic and endogenous factors that can influence vital sign physiomarkers as a predictor for neonatal sepsis.

Factors	Clinical setting/disease states	Outcomes/observations
Medications		
Caffiene[17,18]	Apnea of prematurity	Caffeine stimulates the autonomic nervous system and causes an increase in vagally mediated HRV. Apnea results from brainstem immaturity
Steroid[19]	Severe broncho-pulmonary dysplasia	Dexamethasone improves HRV and lowers the HRC index in preterm infants with chronic lung disease on mechanical ventilation
Inotropic agents[20] (dopamine, vasopressin)	Systemic hypotension	Measures of heart rate variability correlate with the degree of neurohumoral activation in patients with left ventricular dysfunction or heart failure
Atropine[21]	ROP screening	Atropine modulates heart rate and blood pressure variability, suggesting that baroreceptor-mediated parasympathetic control of heart rate is of significance for cardiovascular control in preterm infants
Opioids[22]	Neonatal pain management	Remifentanil can cause bradycardia either by parasympathetic activation or by other negative chronotropic effects
Beta-agonist (albuterol)[23]	Bronchospasm	β_2-adrenoceptor modulated HRV in healthy adult volunteers; the variability was reduced by the β_2-adrenoceptor agonist albuterol
Clinical intervention therapy		
Red blood cell (RBC) transfusion[24,25]	Anemia of prematurity	Organ perfusion and regional tissue oxygenation vary in anemic preterm infants. RBC transfusion improves regional tissue oxygenation and optimizes organ perfusion
Incubator[26]	Immature thermoregulation	Electromagnetic field produced by incubators influence newborns' HRV, showing an influence on their autonomous nervous system
Whole-body cooling— therapeutic hypothermia[27]	HIE	Depressed HRV was significantly associated with adverse outcomes of death or moderate-to-severe abnormalities on EEG or MRI in neonates undergoing therapeutic hypothermia for HIE

HRV heart rate variability, *HIE* hypoxic ischemia encephalopathy.

CHALLENGES OF USING VITAL SIGN METRICS AS A PHYSIOLOGICAL BIOMARKER FOR NEONATAL SEPSIS

In order to assure high standards of neonatal care, the infant's foremost vital signs—temperature, blood pressure, heart rate, and SpO_2—are continuously monitored, but much of the collected information remains unused, despite common appreciation for the predictive power of evaluating time trends in clinical decision-making (which most clinicians do in a subjective, rather than objective, manner). Of note, several confounding variables that modulate vital sign physiomarkers other than neonatal sepsis are outlined by the authors and summarized in the summarized in Table 1.[17–27] The authors acknowledge that (1) associated diagnoses related to prematurity such as anemia, periodic breathing, or apnea of prematurity, (2) medication administration in the NICU as part of the routine hospital stay such as caffeine, atropine, inotropic agents, or opioids, and (3) clinical interventions to treat the diagnoses including red blood cell transfusion, oxygen therapy, or use of an incubator can mask the physiologic response to cardiorespiratory instability and potentially alter the vital sign cues that could otherwise lead to early detection of sepsis.

CHALLENGES OF USING SOPHISTICATED BIOINFORMATIC TOOLS

While clinicians recognize that sepsis detection is heightened by illness predictive scores and laboratory parameters, these measures are freighted with considerable variability related to comorbid illnesses, and lose (population-scale) precision when used to differentiate individual patients, or changes within individual patients over time, at the bedside. Novel preventive strategies that use biotechnology for sepsis prediction also offer challenges. ICUs will require specialized EMR (electronic medical record) systems with advanced data capture, archiving, and analytics, as well as *easily interpreted user interfaces*. EMR documentation of real-time events must permit the use of sophisticated artificial intelligence algorithms through machine learning models for real-time analysis of vital sign dynamics in order to predict future risk for decompensation or cardiorespiratory instability.[25] Institutions will require continuous telemetry equipment for each infant in the NICU and advanced technology to store the immense volume of real-time data. In addition, institutions will require trained and experienced bioengineering personnel to interpret these signals and translate them into meaningful data for the bedside clinician. In other words, a standardized or a uniform methodology must be developed for clinicians to practice the HRV metrics at the bedside.

The ultimate mission of using advanced time-domain bioinformatic datasets extracted from bedside telemetry data is to enrich the predictive monitoring system and assist the bedside clinician in successfully identifying infants at risk for sepsis and preventing morbidity and mortality. It is increasingly recognized that achieving this goal will require integration of the more modern, sophisticated monitoring system initiatives, and summary statistics to the traditional method of physiologic and clinical observations to identify preterm infants at risk for sepsis and provide appropriate treatment. As evidenced by challenges in achieving stable penetration of other "best practices," as simple and uncontroversial as hand-washing, sustained success in achieving this goal requires not only successful tool development but thoughtfully considered implementation of the tools themselves (optimized interface, staff education, mature algorithm development, internal feedback, etc.).[28–30] Until then, clinical application of vital sign physiomarkers in neonatal and infant prognosis and therapy is still "premature." Moving forward, more research must be invested in expanding the machine learning models that utilize bedside vital sign datasets, that recommendations for standardized analytical methods be established, and, importantly, that formal engagement with experts in implementation and dissemination science are engaged proactively in the tool and algorithm development process.

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SS is the first and the corresponding author that drafted the initial article with substantial contribution to conception, design, including analysis and interpretation of data. SS and AD edited the article and revised it critically for important intellectual content prior to submission of the final version.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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