Review

Predictive monitoring for sepsis and necrotizing enterocolitis to prevent shock

Brynne A. Sullivan a, *, Karen D. Fairchild b

a Neonatal/Perinatal Medicine, University of Virginia School of Medicine, Charlottesville, VA, USA
b Division of Neonatology, University of Virginia School of Medicine, Charlottesville, VA, USA

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SUMMARY

Despite vigilant clinical assessment of infants in the neonatal intensive care unit (NICU), diagnosis of sepsis and necrotizing enterocolitis often does not occur until an infant has significant hemodynamic compromise. Predictive monitoring involves analysis of vital signs and other clinical data to identify infants at highest risk and to detect early-stage illness, leading to timelier treatment and improved outcomes. The first vital-sign predictive monitoring device developed for sepsis detection in babies in the NICU is the heart rate characteristics index (HeRO) monitor, which continuously analyzes the electrocardiogram signal for low heart rate variability and transient decelerations. Use of this monitor in very low birth weight infants (<1500 g) was shown in a large multicenter randomized clinical trial to significantly reduce mortality. The purpose of this review is (1) to summarize the physiologic changes in neonatal sepsis and progression to shock, (2) to review efforts toward risk stratification for sepsis shortly after birth based on demographic and physiologic scoring systems, (3) to describe development and implementation of heart rate characteristics monitoring and other important aspects of sepsis early warning systems, and (4) to provide an overview of current research analyzing multiple vital signs and other clinical variables in an attempt to develop even more effective predictive monitoring devices and systems.

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1. Introduction

Shock is an uncommon but potentially deadly consequence of sepsis and/or necrotizing enterocolitis (NEC) in preterm infants. Immature host defense mechanisms predispose neonates to focal and systemic infections which may be contained for a short period of time, but, if left untreated, may progress to fulminant sepsis. The term “sepsis” denotes both evidence of infection and vital sign changes indicating a systemic inflammatory response syndrome (SIRS). In SIRS, pathogens activate inflammatory pathways resulting in release of cytokines and other mediators that cause damage to cells and tissues. SIRS is well defined in adults and children and requires the presence of two or more of the following: tachycardia, tachypnea or respiratory alkalosis, fever or hypothermia, and high or low white blood cell count or bandemia. The International Pediatric Sepsis Consensus Conference has defined the continuum including SIRS, sepsis, severe sepsis, shock, and multiple organ dysfunction in the first week, first month, and first year after birth for infants born at term [1]. These definitions have limited applicability for identifying early-onset sepsis and do not translate well to preterm infants in whom abnormal vital signs such as tachypnea and hypotension may reflect immature organ systems or a developmentally regulated limited ability to attenuate non-specific inflammation rather than SIRS or sepsis [2,3]. SIRS criteria specific to preterm infants have been suggested but require further evaluation [4].

Like SIRS, the term “shock” is not well defined in NICU patients but is generally taken to indicate poor systemic and tissue perfusion, which are often associated with tachycardia, hypotension, and metabolic acidosis. Two common causes of shock in the NICU are septicemia and NEC, with about 5% of infants with late-onset sepsis and up to half of those with NEC presenting with or progressing to shock [4,5]. Gram-negative bacteria, which account for about 20% of cases of late-onset septicemia in VLBW infants, are more likely to
lead to shock and death than Gram-positive bacteria [6,7]. Viruses such as herpes simplex virus and enteroviruses in neonates can also lead to septic shock with high mortality [8]. Delayed or inadequate treatment of infection may contribute to progression to septic shock, which may in turn lead to transient or permanent organ damage or death [9].

2. Conventional approach to sepsis and NEC detection

Since sepsis and NEC are relatively common among preterm infants, NICU practitioners are on the lookout for signs of these illnesses. A typical scenario is that a caregiver, usually the bedside nurse, notices that a preterm infant is “not acting right” with clinical signs such as increased frequency or severity of apnea episodes, decreased activity, or feeding intolerance. These findings are common in non-septic preterm infants, and it is difficult to determine whether there is a change from the baby’s baseline, even for very experienced practitioners. Thus, cultures are obtained and antibiotics administered for many infants. Reliability of culture results may be limited in neonates by low sampling volume for blood [1], by sampling method for urine, and by administration of antibiotics before cultures are obtained for cerebrospinal fluid. Use of biomarkers to aid in detection of true sepsis has been extensively studied [10], with C-reactive protein (CRP) remaining the most widely used acute phase reactant [11]. The drawback of biomarkers as currently used is that they can be elevated in non-specific inflammatory processes, are not continuously available and are generally tested only after the infant develops concerning signs and symptoms, which, in some cases, may be too late. Combining biomarker screening with predictive monitoring of physiologic markers for assessing risk of sepsis or NEC and for detection of early-stage illness could, at least theoretically, prevent progression to severe illness and shock.

The goals of predictive monitoring are two-fold: (i) to identify patients at high risk for life-threatening morbidities, and (ii) to detect early-stage illness in order to shorten the time to medical treatments that could reduce morbidity and mortality (Fig. 1).

3. Risk assessment for sepsis and NEC

Whereas preterm infants are all inherently at high risk for infection, identifying those at highest risk early in their NICU stay could allow caregivers to target them for heightened surveillance or preventive interventions that might not be appropriate for the entire population. Demographic variables such as gestational age and postmenstrual age as well as clinical variables such as invasive tubes, lines, and therapies increase risk for infection. Male sex and black maternal race are associated with increased infection-related mortality in low birth weight infants [12]. For NEC risk assessment, a recent report describes a composite score, “GutCheckNEC”, that includes nine independent risk factors, including fixed variables such as gestational age, unit NEC rate, race, and outborn status together with factors that may change the score during a patient’s hospital course, including blood transfusion, late-onset sepsis, multiple infections, need for pharmacologic blood pressure support, and metabolic acidosis. Two risk reducers, exclusive human milk feeding and probiotic administration, were also factored into the score. The score was derived from data from about 35,000 infants, calibrated in 23,000 infants, and validated in 120 NEC cases compared to 240 matched controls and shown to discriminate infants that developed severe NEC (receiver operating characteristics area under the curve: 0.83) [13].

Genomic or biomarker screening might also identify high-risk NICU patients. Genomic variations that impact cytokine production and cell signaling pathways have been reported to be associated with increased susceptibility to neonatal sepsis [14,15] and a...
Physiologic measurements shortly after birth also have potential to assess risk for later development of sepsis or NEC. Well-known risk scores in NICU patients include the Score for Neonatal Acute Physiology (SNAP) and Clinical Risk Indicator for Babies (CRIB), which were developed to predict mortality based on demographic and physiologic variables. Although these illness severity scores are likely to be high in infants with early-onset sepsis and shock in the first day after birth, they have not been shown to predict later development of sepsis or NEC. A score incorporating gestational age, birth weight, and mean and standard deviation of heart rate, respiratory rate, and oxygen saturations in the first 3 h after birth was reported to be significantly associated with development of late-onset sepsis in a study of 138 preterm infants [17]. Low heart rate variability in the first week after birth was also found to be associated with development of NEC in a study of 70 preterm infants [18]. Further studies in larger populations of preterm infants that test various combinations of demographic and physiologic variables for their ability to predict development of sepsis and NEC will provide valuable information for clinical care and morbidity prevention.

4. Conventional vital sign monitoring in the NICU

Conventional bedside monitors display current vital signs, and alarms are activated when parameters are outside a range considered to be normal. This is the simplest, most basic form of physiologic monitoring, and has a number of limitations for detection of early stages of illness:

1. “Normal” vital signs for the population may not apply to individual patients.
2. Alarms are not always clinically important, and caregivers do not always respond appropriately to alarms.
3. Trends in vital signs over time are not displayed, and there is limited ability to review events or store data for analysis.
4. Less experienced clinicians may not know how to interpret and act on “out of range” vital signs.
5. Abnormal patterns, such as a decline in heart rate variability from a patient’s baseline, cannot be discerned from conventional monitors.

5. Analysis of complex vital sign patterns for earlier illness detection

In sepsis, preterm neonates’ vital signs may go in either direction: tachypnea or apnea may occur, hypothermia is more common than fever, and heart rate may be elevated or depressed in different phases of illness. Another diagnostic challenge in extremely preterm infants is that low blood pressure, apnea, tachycardia, hypothermia, and other vital sign changes are common in non-septic preterm infants due to physiologic immaturity and the developmentally regulated decreased ability to attenuate a non-specific inflammatory response. Clinicians must therefore be vigilant in assessing vital signs compared to an individual baby’s baseline. Automated systems to alert clinicians to abnormal trends in vital sign patterns that might signal impending illness could lead to earlier therapies and improved outcomes.

A vital sign-based early warning system for sepsis would ideally involve analyzing a signal that is continuously available and reliable in all NICU patients, and one that is known to change early in the course of a systemic inflammatory response. Blood pressure is continuously monitored by arterial catheters early in the NICU stay of many extremely preterm infants, but typically when sepsis or NEC develops at several weeks of age the infant no longer has an umbilical or peripheral arterial catheter. Thus, blood pressure, which later in the course is measured infrequently, is not a good early indicator of sepsis. Temperature is continuously monitored, but preterm infants are in incubators that automatically adjust environmental temperature to keep the infants’ temperature in the normal range; thus, fever or hypothermia due to illness may be masked. Analysis of respiratory rate to assess for tachypnea or apnea is confounded by inaccuracy of chest impedance signal and by the fact that many infants are on mechanical ventilation at the time of diagnosis of sepsis or NEC. Oxygen saturation detected by pulse oximeter is continuously available in all NICU patients but acute changes in SpO2 have not been studied for their association with sepsis or NEC. This leaves the electrocardiogram, which is continuously available and contains useful information about health and illness, as an ideal signal for predictive monitoring.

6. Heart rate characteristics analysis

Heart rate is regulated by the autonomic nervous system and is influenced by immunologic and cardiovascular changes; as such, heart rate patterns can be an indicator of pathologic processes including sepsis. Research in both adults [19] and preterm infants [20] indicates that low heart rate variability (HRV) occurs in sepsis, often before obvious clinical signs are recognized. In neonates, in addition to overall low variability, transient decelerations in heart rate were discovered in the hours leading up to diagnosis of sepsis [21]. The following sections review pathophysiology of these abnormal heart rate patterns, development and testing of a monitor that reports on both low variability and transient decelerations, results of a randomized clinical trial, and practical applications of the monitor.

6.1. Mechanisms of abnormal heart rate characteristics in sepsis

In a healthy state, sympathetic nerve firing leads to norepinephrine release, which acts at sinoatrial node pacemaker cells to cause a small increase in heart rate, and parasympathetic firing leads to acetylcholine release, which leads to a transient deceleration. Decreased heart rate variability occurs in a number of pathophysiologic conditions including sepsis [22]. Animal studies in both prenatal and postnatal models have shown that pathogen toxins such as lipopolysaccharide from Escherichia coli can dampen heart rate variability, in part through pro-inflammatory cytokines [23,24]. In a study of 226 infants at two NICUs undergoing evaluations for suspected late-onset sepsis, there was an association between elevated plasma cytokines, an elevated HRC index (reflecting low heart rate variability), and growth of bacteria in blood culture, particularly in cases of Gram-negative septicemia [25].

Depressed heart rate variability is one component of the HRC index, and transient heart rate decelerations is another [26]. Apnea increases in some preterm infants with sepsis and contributes to the decelerations captured by the HRC index, but these decelerations also occur in septic infants on mechanical ventilation. Studies in a mouse model revealed that administration of bacteria or candida rapidly leads to vagus nerve signaling and to transient, repetitive heart rate decelerations [27]. The vagus nerve is critical to innate host defense through the cholinergic anti-inflammatory pathway, which dampens inflammatory cytokine production by leukocytes and enhances survival [28]. It is tempting to speculate that transient heart rate decelerations in neonates with sepsis reflect activation of this important vagus nerve-mediated host defense mechanism.
6.2. Development of the HRC index (HeRO score)

Given the observation of decreased variability and decelerations in preterm infants with sepsis, an HRC index was developed using a mathematical algorithm designed to detect the fold-increase in risk of an infant developing sepsis in the next 24 h. The HRC index incorporates three things: a simple measure of heart rate variability (standard deviation of R–R intervals); a measure that accounts for the presence of abnormal heart rate decelerations (sample asymmetry) [29]; and a measure of complexity (sample entropy) [30]. The mathematics behind development of the HRC index have been extensively described and reviewed [31] and are beyond the scope of this review. Of note, the index does not account for differential changes in high- and low-frequency heart rate variability (HF-HRV, LF-HRV). There is an extensive literature suggesting that HF-HRV reflects parasympathetic (vagal) tone and that LF-HRV reflects sympathetic tone, but there is also considerable debate over the relevance of this distinction, particularly in preterm infants with generally fast and irregular respiratory rates that confound measurement of HF-HRV. Regardless, in developing the HRC index it was shown that both LF-HRV and HF-HRV decrease in equal proportions in septic preterm infants [32].

The HRC index or “HeRO score” was developed at the University of Virginia in >300 VLBW infants with >100 episodes of sepsis. It represents the fold-increased risk that a baby will be diagnosed with culture-proven or clinical sepsis in the next 24 h, compared to the risk for all VLBW infants within the NICU stay. The index was externally validated at Wake Forest University in a similar number of infants and was again shown to be highly correlated with diagnosis of sepsis [33,34]. Subsequent studies showed that a high HRC index (“HeRO score”) is also correlated with mortality and with other infections and adds to laboratory values in the diagnosis of sepsis [35,36].

The HeRO (Heart Rate Observation) monitor (Medical Predictive Science Corporation, Charlottesville, VA, USA) received 510K clearance by the US Food and Drug Administration in 2003 for monitoring heart rate characteristics in infants and children and was CE-marked for use in Europe in 2012. The monitor analyzes the electrocardiogram data from standard NICU monitors in real time and continuously displays the HRC index, which is updated hourly and reflects heart rate variability and transient decelerations in previous 12 h. It displays the current HRC index, the trend over the last five days, and the last 30 min of heart rate (Fig. 2). Users may choose to view a display from an individual baby, multiple babies in a pod, or all babies in the unit.

From 2004 to 2010, a multicenter randomized trial was conducted to determine the impact of heart rate characteristics monitoring on outcomes of very low birth weight infants (<1500 g), with 3003 infants enrolled in nine NICUs. All infants in the study had continuous HRC index monitoring and half were randomized to having the index displayed to clinicians whereas the other half had only conventional monitoring displayed. There were no mandated interventions for a rise in the HRC index; clinicians were simply instructed in how the index was developed and encouraged to examine a baby with a rising score. The major finding was a 22% relative decrease in mortality for patients randomized to having the HRC index displayed (10.2% vs 8.1%, P = 0.04) [37]. In a subsequent analysis of 974 cases of blood culture-positive sepsis among the 3003 infants in the trial, mortality within 30 days of septicemia was 40% lower in the heart rate characteristics display compared to the HRC-blinded infants (19.6% versus 11.8%, P < 0.01) [38].

Although the HRC index monitor was not specifically designed for detection of NEC, the pathophysiology of sepsis and NEC overlap to some extent, and it seems likely that some infants with NEC will manifest abnormal heart rate characteristics in the early phase of illness. Indeed, in a study of 97 infants with NEC at three
centers participating in the RCT, there was a significant rise in the HRC index over patients’ baseline on average 6 h before clinical detection of medical NEC and 16 h before diagnosis of surgical NEC [39].

### 6.3. Challenges associated with HRC index monitoring

The HRC index does not replace clinical judgment, and NICU caregivers must learn to use the system appropriately to avoid overuse of antibiotics and to ensure appropriate treatment of neonates with significant signs of sepsis irrespective of the HRC index. In the RCT, overall use of antibiotics increased 5%, and 10% more blood cultures were obtained in infants whose HRC index was continuously displayed at the bedside. Focusing specifically on the 700 infants who experienced at least one episode of blood culture-positive sepsis, average number of days on antibiotics for the entire NICU stay was 32 in the HRC display group compared to 29 in the control group [38]. In this sub-analysis, the fact that antibiotic use was only increased 10% whereas sepsis-associated mortality decreased 40% suggests that perhaps antibiotic therapy was timed more appropriately in the HRC display group.

In making decisions about management of infants with a rising HRC index it is important to consider that abnormal heart rate characteristics are not specific to bloodstream infection and may occur in other infectious and non-infectious conditions. An analysis of all large increases in the HRC index of infants in the control arm of the RCT at a single center was performed to determine clinical associations with a “spike,” defined as an increase of two or more points over the prior five-day baseline. Spikes commonly occurred following surgery, including minor procedures with no complications, likely due to a combination of anesthetic effects and an acute phase response to tissue trauma (see Case 4). Excluding cases of surgery, 53% of HRC index spikes were associated with suspected or proven infection (including urinary tract infection) or NEC. Thirty-four percent of the spikes were associated with acute respiratory deterioration without infection [40]. In some infants, there were increased apneic spells with associated heart rate decelerations but in other cases infants were on mechanical ventilation, in which case the abnormal heart rate characteristics may have been due to acute lung inflammation, respiratory acidosis, or hypoxemia. Finally, 13% of large HRC index spikes had no apparent clinical correlation. This highlights the principle that the HRC index should not stand alone as a trigger for antibiotic therapy but should be incorporated into all other clinical and laboratory information for decision-making.

Another challenge of heart rate characteristics monitoring is that infants with severe chronic illness tend to have a chronically elevated score. For example, infants with grade III–IV intraventricular hemorrhage [41] and those with significant lung disease [40] may have a high score with frequent spikes for several weeks after birth (see Case 4). For infants with a chronically elevated HRC index, other clinical variables and laboratory tests must be used in decisions about obtaining cultures and administering antibiotics.

Most medications administered to NICU patients have no apparent effect on the HRC index. Notable exceptions include atropine which transiently dampens heart rate variability and increases the HRC index, and dexamethasone which improves heart rate variability and lowers the HRC index.

### 6.4. Practical application of HRC index monitoring

The following cases and the HRC index monitor screen shots in Fig. 2 demonstrate how the monitor may be useful in day-to-day management of preterm infants in the NICU.

#### 6.4.1. Case 1 (Fig. 2A)

A 29-week gestation infant spends seven weeks in the NICU, has no major complications associated with prematurity, and his HRC index is generally low (normal).

#### 6.4.2. Case 2 (Fig. 2B)

A two-week-old 29-week gestation infant has feeding intolerance and apnea. On examination, she has abdominal distension and the HRC index is mildly elevated over her baseline. Feeds are stopped and antibiotics started. Radiographs and laboratory tests are normal, the HRC index remains <2, NEC is ruled out, antibiotics discontinued, and feeds restarted.

#### 6.4.3. Case 3 (Fig. 2C)

A four-week-old 24-week gestation infant has had an HRC index between 1 and 2 for several days. The nurse notes a rise in his HRC index to 3 and alerts other team members. Physical examination is unremarkable but he is noted to have more apnea than his baseline. Cultures are obtained and antibiotics started. His blood and urine cultures yield *Klebsiella pneumoniae*.

#### 6.4.4. Case 4 (Fig. 2D)

A four-week-old 24-week gestation infant has a high HRC index in the first day after birth. He develops a grade 3 intraventricular hemorrhage and chronic lung disease and has an HRC index ranging from 2 to 4 for several weeks. He occasionally has cultures sent and antibiotics given for clinical deterioration but has no episodes of culture-proven infection. By five weeks of age his HRC index has normalized and remains low except for an acute increase after uncomplicated surgery to repair an inguinal hernia.

### 7. Respiratory analysis for sepsis and NEC detection

Additional vital sign analysis might improve on heart rate characteristics analysis for early detection of sepsis and NEC. Increased central apnea is a frequent presenting sign of infection and sepsis in preterm infants, with preclinical mechanistic studies showing increase in pro-inflammatory cytokines in the brainstem leading to sepsis-associated apnea [42]. Detection of central apnea by standard NICU bedside monitors involves analysis of chest impedance waveforms and is known to be inaccurate. A new central apnea detection system was developed by the research group that developed the HRC index monitor and involves filtering motion and cardiac artifact out of the chest impedance signal to more accurately identify number and severity of central apnea events [43]. Quantitation of central apnea or of temporally associated drops in heart rate and SpO2 as a surrogate indicator of apnea may allow prediction of impending clinical deterioration and might add to the diagnostic value of heart rate characteristics analysis for early detection of sepsis and NEC. Detecting a decline in normal cardio-respiratory interactions such as cardiorespiratory coupling (increase in heart rate during inspiration) or cardioventilatory coupling (synchronization of breaths with heart beats) may also provide insights into impending clinical deterioration [44].

### 8. Alert systems and rapid response teams

Translating new predictive monitoring devices to improvement in patient care requires a process for alerting caregivers to an acute worsening in a patient’s status. In the case of the HRC index monitor, there are no audible alarms and caregivers must devise a system to alert the medical team about an acute rise in an infant’s HRC index. Typically, this involves the nurse recognizing a rise in the score of one or more points over the infant’s baseline and informing the medical team of the change. The team can then...
examine the baby, consider clinical signs observed by bedside caregivers (usually the nurse and sometimes the mother), review trends in vital signs and laboratory values, and determine a course of action. In some cases the best course of action is close surveillance for any signs of deterioration, whereas in others, obtaining cultures and initiating antibiotic therapy might be indicated.

Other early warning systems to detect and respond to clinical deterioration have been developed for pediatric and adult populations and usually include some number of vital sign and laboratory abnormalities triggering notification of bedside caregivers and a rapid response team. Depending on the number of SIRS criteria and the thresholds for laboratory values such as serum lactate, these systems have a wide range of sensitivity and false positives [45, 46]. Implementation of these early warning systems in various hospital settings has led to improved outcomes, including decreased time to antibiotic administration [47] and less progression to multi-organ failure [48]. For infants and children, the Pediatric Early Warning System (PEWS) was developed as a tool for bedside caregivers to assess cardiorespiratory and neurologic deterioration but its impact on sepsis-related outcomes has not been tested [49]. With regard to neonates, a “Neonatal Trigger Score” based on level of consciousness, respiratory rate, heart rate, and temperature identified infants >35 weeks of gestation who subsequently required intravenous fluids, respiratory support, and/or NICU admission [50]. Although none of these scores addresses early detection of sepsis in preterm infants in the NICU, they illustrate the concepts of combining analysis of vital signs and other parameters into a score that triggers closer evaluation of patients to prevent further deterioration.

A “Preterm Sepsis/NEC Alert” could include some or all of the variables on the following list. Note that values out of normal range for gestational and postmenstrual age would be desirable and an acute change from an individual patient’s baseline would be ideal.

1. A measure of abnormal respiratory rate (tachypnea, apnea).
2. A measure of abnormal heart rate (consistent tachycardia or consistent or repetitive transient bradycardia).
3. A measure of abnormal heart rate characteristics, such as the HRC index.
4. A measure of clinical signs such as new onset of feeding intolerance.
5. A measure of physical examination abnormalities such as absent bowel sounds.
6. A measure of poor perfusion such as delayed capillary refill time, low urine output, or low blood pressure.
7. A measure of abnormal laboratory values such as acute phase reactants, if these studies are available and clinically indicated.
8. A measure of abnormal radiographic findings, if studies are indicated.

9. Advanced hemodynamic monitoring in preterm infants with sepsis and NEC

Once preterm infants are diagnosed with suspected sepsis or NEC, advanced hemodynamic assessment tools, including near-infrared spectroscopy (NIRS), electrical cardiometry, and functional echocardiography could be useful to monitor for clinical deterioration and guide fluid and vasopressor-inotrope therapy [51]. The role of these and other tools such as pulsatility index of the photoplethysmography (pulse oximeter) signal for risk assessment or early detection of sepsis and NEC deserves further study.

10. Conclusion

Monitoring heart rate characteristics for signs of imminent sepsis was shown to reduce mortality among VLBW infants. Adding new vital sign and hemodynamic metrics and integrating laboratory values, biomarkers, and clinical information could lead to even better algorithms for early sepsis detection. As new technologies or sepsis alerts are developed, training healthcare providers in how to interpret them and testing their impact on clinically meaningful outcomes should be a high priority toward improving outcomes of preterm infants.

Practice points

- The heart rate characteristics (HeRO) monitor analyzes bedside monitor electrocardiogram signal for decreased variability and transient decelerations and displays a score that is the fold-increased risk of sepsis in the next 24 h for VLBW infants.
- Heart rate characteristics monitoring reduced all-cause mortality by 22% and sepsis-associated mortality by 40% in a randomized clinical trial of 3003 VLBW infants.
- Abnormal heart rate characteristics are not specific to bloodstream infection and may occur in other infectious and non-infectious conditions.
- Implementing a system for alerting clinicians to abnormal vital signs or predictive monitoring scores may lead to earlier initiation of therapy for sepsis or NEC.

Research directions

- Test the ability of vital sign-based scores soon after birth to identify infants at highest risk for adverse outcomes such as late-onset septicemia or NEC.
- Add analysis of other vital signs including respiratory rate and oxygen saturation to heart rate characteristics analysis to determine optimum metrics for detection of early-stage sepsis or NEC.

Conflict of interest statement

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References


