Review Article

A narrative review of heart rate and variability in sepsis

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Abstract: Clinicians face challenges in the timely diagnosis and management of pediatric sepsis. Pediatric heart rate has been incorporated into early warning systems and studied as a predictor for critical illness. We aim to review: (I) the role of heart rate in pediatric warning systems and (II) the role of heart rate variability (HRV) in adult and neonatal sepsis, with a focus on its potential applications in pediatrics. We conducted a literature search for papers published up to December 2019 on the utility of heart rate and HRV analysis in the diagnosis and management of sepsis, using four medical databases: PubMed, Google Scholar, EMBASE and Web of Science. This review demonstrates that the clinical utility of pediatric heart rate in predicting clinical deterioration is limited by the lack of consensus among warning systems, consensus-based guidelines, and evidence-based studies as to what constitutes abnormal heart rate in the pediatric age group. Current studies demonstrate that abnormal heart rate itself does not adequately discriminate children with sepsis from those without. HRV analysis provides a quick and non-invasive method of assessment and can provide more information than traditional heart rate. HRV analysis has the potential to add value in identification and prognostication of adult and neonatal sepsis. With further studies to explore its role, HRV analysis has the potential to add to current tools in the diagnosis and prognosis of pediatric sepsis.

Keywords: Heart rate; sepsis; shock; critical care; early warning scores

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Introduction

Pediatric sepsis, a serious and potentially lethal condition, remains an important cause of morbidity and mortality (1). The World Health Organisation (WHO) estimates that 1.2 million children suffer from sepsis every year (2), and infections account for more than half of the deaths in children under 5 years old (3). While isolating the offending agent allows for definitive management, microbiological investigations usually take about 24–72 hours to return and are often influenced by factors including the adequacy of blood volume taken and the presence of low, transient bacteraemia (4,5). Therefore, early identification of patients with sepsis cannot rely on microbiology investigations alone (6); accurate prediction of which child has sepsis remains a clinical challenge.

The 2018 update to The Surviving Sepsis Campaign Bundle included an "hour-1 bundle" to be achieved within one hour from the time of triage in the Emergency Department (ED) (6). Clinicians need to be able to quickly identify a critically ill child and administer treatment protocols without definitive blood culture results. Many clinicians define pediatric sepsis based on the systemic inflammatory response syndrome (SIRS) criteria established by Goldstein in 2005 to identify a critically ill child with sepsis (7). However, the SIRS criteria has limited clinical

applicability. A recent study showed that most children who fulfil the SIRS criteria do not require critical care, and many children who required resuscitation did not meet the SIRS criteria at the time of presentation (8). Moreover, identification of a septic child is often complicated by its heterogeneous clinical presentation, which can range from a non-specific presentation like fever, irritability, and poor feeding to fulminant sepsis with hemodynamic compromise (9).

The need for an objective assessment in pediatric critical illness has led to the use of vital signs. Vital signs have been and continue to be extensively studied as part of triage systems and warning scores (10-16). Scoring and triggering systems which include heart rate have been used to predict potential deterioration and the need for intensive care (17). Other investigators have attempted to define normal ranges for heart rate, built on the understanding that an abnormal heart rate is an important indicator of critical illness, including sepsis (18-20). As such, heart rate parameters are attractive to clinicians in that they can potentially add to the timely recognition of pediatric sepsis.

This review seeks to: (I) review the role of heart rate in pediatric warning scores, including its role as a predictor for critical illness including sepsis; and (II) introduce the concept of heart rate variability (HRV) analysis. In this review, we will highlight the current uses of HRV analysis (including in adult and neonatal sepsis) and explore how it can be utilized in pediatric sepsis. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/atm-20-148).

Methods

We conducted a literature search for papers published up to December 2019 on the utility of heart rate and HRV analysis in the diagnosis and management of sepsis, using four medical databases: PubMed, Google Scholar, EMBASE and Web of Science. Study selection was based on three medical databases, PubMed, EMBASE and Web of Science, with the following search strategy (including specific Medical Subject Headings, MeSH): "heart rate/physiology", "sepsis/diagnosis", "sepsis/mortality" and "sepsis/complications". Other free text terms used were: "heart rate variability", "emergency medical service", "critical care", "intensive care unit", "neonate", "infant" and "child". Qualitative and quantitative data were extracted through interpretation of each article in cycles to avoid missing on data of potential value.

Discussion

Heart rate as a predictor for critical illness including sepsis

Heart rate is an easily obtained parameter that many clinicians use as an early marker of deterioration in children. Various hospitals have developed pediatric early warning systems (PEWS) (10-13). A large systematic review of 66 studies of various PEWS and its derivatives demonstrated limited evidence of PEWS in identifying children with impending clinical deterioration (16). Of note, there was marked heterogeneity of outcome metrics, interventions, populations and clinical settings in the various studies (16). Categorical examples with their respective heart rate reference ranges can be found in *Table S1*, where we compare age-related thresholds for abnormal heart rate in selected PEWS scores to currently published heart rate guidelines and threshold limits used in large cross-sectional studies.

Although heart rate is a convenient and easily accessed physiological parameter, there is a lack of consensus among warning scores on what constitutes significant, out-of-proportion tachycardia in a sick child (*Table S1*). For instance, the normal heart rate of a 8-year-old child is between 80 to 120 bpm according to APLS guidelines, and PALS places the normal heart rate of a 8-year-old child at between 60 to 140 bpm (21,22).

There have been multiple attempts to define a normal heart rate range for different age groups in large and robust study populations (18-20). When one considers the normal ranges of heart rate based on these population studies, the heart rate ranges in various PEWS scores may not necessarily be representative of a "sick" child. This is especially so for PEWS scores that incorporate wide age bands. We know that with increasing age comes a steady decrease in heart rate. Consequently, these PEWS scores may result in false positive triggers (18-20). If implemented into monitoring systems, it can result in unnecessary resource utilisation, poor performance of scoring and triggering systems, and ultimately alarm fatigue (23). This creates a conundrum fundamental to the importance of heart rate as a vital component of prediction scores.

Tachycardia out of proportion to age and height of fever has also been proven not to have good discriminatory value in the prediction for infants with sepsis (24). Multiple contributors to tachycardia including pain, anxiety, and

fever limit the interpretation of this important vital sign in children. It is recognized that continuously measured physiologic variables and their trends may better inform monitoring strategies for critically ill children with different admission diagnoses (including sepsis) (25).

The clinical value of traditional heart rate as a predictive tool is thus limited, and this has led to the exploration of novel methods such as HRV analysis.

Heart rate variability (HRV)

The study on measuring heart rate and rhythm has progressed from cardiac auscultation, the advent of the galvanometer (used to detect and measure small electric currents), to the era of digital signal processing systems such as the electrocardiogram (ECG). It was through the 1996 report of the Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology that a novel method of HRV analysis was definitively introduced (26). HRV analyzes the oscillation in the interval between consecutive heart beats (RR interval), and is a measure of autonomic nervous system (ANS) regulation (27). ANS dysfunction is a maladaptive response in injury and critical illness, including sepsis (27). In the past few decades, more studies have delved into the relationship between HRV as a measure of ANS dysfunction, and various critical illnesses (26,28).

HRV parameters

Data collected from an ECG over a continuous time-period forms the basis for HRV analysis. *Figures 1* and *2* show the difference between a patient with good heart rate variability and one without.

The three domains employed in HRV are the time-domain; frequency-domain; and the non-linear domain. Time-domain parameters are derived from measuring the normal "RR intervals", otherwise known as "NN intervals", or from the differences between NN intervals. In practice, these three measurements are often used interchangeably. Frequency-domain parameters measure how often a signal recurs within a specific frequency band, and this is derived from spectral analysis. Non-linear methods are a means to explain the complex interactions of HRV involving the hemodynamic, electrophysiological and humoral variables, and our autonomic and central nervous system (26). Many of these parameters are well-described in the report of the Task Force (26). Some of the parameters discussed in this report are listed in *Table 1*.

Current applications of HRV

The clinical applications of HRV analysis are well documented in the practice of adult cardiology. Reduced HRV in adults is predictive for sudden cardiac death (29-31), increased mortality after an acute myocardial infarction (26,32,33), and is deemed an independent risk factor for developing cardiovascular diseases (34,35). In recent years, as a risk stratification tool in chest pain, HRV has been consistently demonstrated to outperform commonly used validated scoring systems [e.g., thrombolysis in myocardial infarction (TIMI) score, patient acuity category scale (PACS), and the modified early warning score (MEWS)] (36,37). In diabetes mellitus, patients with diabetic autonomic neuropathy demonstrated a reduced low frequency/high frequency (LF/HF) ratio (38) and this reduction in variability preceded clinical symptoms of diabetic neuropathy (39,40). In anesthesiology, reduced HRV is also associated with the risk for developing hypotension following general anesthesia induction (41). In sepsis, HRV analysis has been studied in the adult and neonatal setting with promising results when compared to traditional heart rate alone. In the next two subsections, we will describe the use of HRV analysis in these settings and explore how these methods can be potentially applied in pediatrics.

Adult sepsis

In adult sepsis, HRV analysis has paved the way for the development of new scoring systems, such as the Singapore Emergency Department Sepsis (SEDS) model (42). The SEDS model, which includes HRV-derived parameters (mean NN and DFA alpha-2) and other parameters such as age, respiratory rate and systolic blood pressure, was shown to outperform the qSOFA score, MEWS and NEWS in predicting 30-day in-hospital mortality for adults with sepsis (42). This was followed by a subsequent study which outlined the high performance of a HRV-based machine learning model in predicting 30-day in-hospital mortality among suspected sepsis patient in the ED (43).

Specific HRV parameters to predict sepsis in the ED have also been explored. An increased square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD) was found in patients who developed septic shock within 6 hours of presentation at the

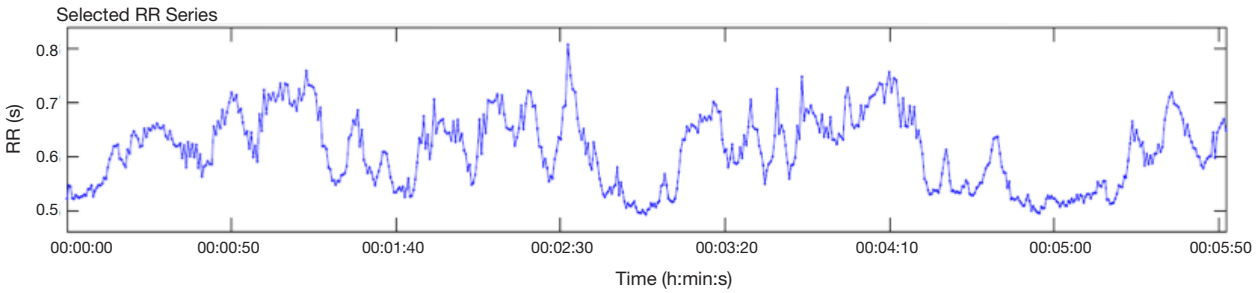

Figure 1 Subject with high heart rate variability (HRV).

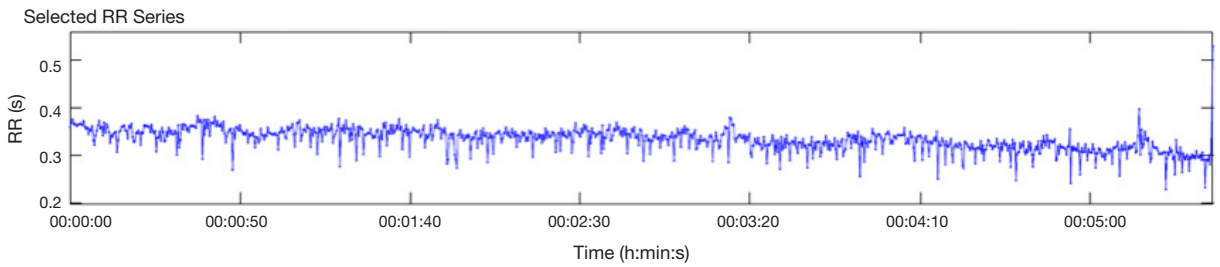

Figure 2 Subject with reduced heart rate variability (HRV).

Table 1 Commonly used HRV parameters for statistical analysis

Time-domain parameters	Frequency-domain parameters	Non-linear domain parameters
Standard deviation of all NN intervals (SDNN)	Very-low-frequency (VLF)	Approximate entropy/sample entropy
Square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD)	Low-frequency (LF)	De-trended fluctuation analysis (DFA-α1/α2)
Number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording (NN50 count)	High-frequency (HF)	Fourier spectra
NN50 count divided by the total number of all NN intervals (pNN50)	LF/HF ratio	Poincare section (i.e., SD1, SD2)
Baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all NN intervals (TINN)		

HRV, heart rate variability.

ED (44). Reduced RMSSD has also been shown to predict for 28-day mortality in septic patients presenting at the ED (45). Some prior studies demonstrated that a decreased LF/HF ratio of less than 1.0 may predict severity of illness in septic patients (46,47). When integrated with various components of other warning scores, HRV parameters have been found to be superior in risk-stratifying septic patients at the ED (48). In the adult intensive care units (ICU), the use of artificial intelligence has allowed HRV parameters to be incorporated into systems and scores that detect sepsis and severe sepsis (49-51). Continuous HRV monitoring has reduced the gap between the onset of sepsis and its clinical recognition by up to five hours, allowing clinicians to direct early intervention efforts in sepsis treatment (52-54).

Given current research efforts, scoring systems incorporating HRV parameters may outperform those with traditional heart rate alone (*Table 2*). Short-term HRV analysis is a potential game-changer in better diagnostic accuracy for adult sepsis in the ED and ICUs and should be integrated with other vital signs obtained at triage for better

Table 2 Studies evaluating the use of HRV in adult sepsis

Author of study	Year of study	Study population	Number of HRV parameters analysed	Relevant HRV parameters			Conclusions	Limitations
				Time domain	Frequency domain	Non-linear		
Samsudin *et al*. (42)	2018	214	22	Mean-NN		DFA-α2	The Singapore ED Sepsis (SEDS) model for mortality, which incorporates respiratory rate, systolic blood pressure and two HRV parameters (mean-NN and DFA-α2), performed best in predicting for 30-day in-hospital mortality (IHM) and adverse events with a ROC curve of 0.78, compared to an AUC of 0.70, 0.70 and 0.56 by qSOFA, NEWS and MEWS score respectively	Single-center study in Singapore
Chiew *et al.* (43)	2019	214	22	SDNN, RMSSD, TINN	LF, HF	DFA-α2, approximate entropy, SD1, SD2	The gradient boosting model performed best with a ROC curve of 0.35, compared to the SEDS (0.22) model, qSOFA (0.21), NEWS (0.28) and MEWS (0.25) score in predicting for 30-day IHM. Top predictors for 30-day mortality included temperature, detrended fluctuation analysis (DFA) a-2, heart rate, Glasgow Coma Scale (GCS) score and approximate entropy. DFA-α2 is the most important HRV parameter in predicting for 30-day IHM	Single-center study in Singapore. Identical database employed by Samsudin *et al*.
Chen *et al.* (44)	2007	81	10	RMSSD	LF, HF, LF/HF ratio		Patients who eventually developed septic shock within 6 hours of presentation were found to have an increased RMSSD and HF and decreased LF and LF/HF ratio. Among the HRV parameters analysed, a raised RMSSD [median =0.78 (4.2–8.7), P<0.01] may be best at predicting for impending septic shock	Single-center study in Taiwan
Bonjorno *et al*. (45)	2019	60	14	RMSSD		SD1	HRV measures, specifically a RMSDD threshold of 10.8 ms were optimal at discriminating survivors and non-survivors with sepsis with a mean survival time difference of 9.9 days	Small sample size. Single-center study in Brazil. Performed in intensive care unit setting. Findings may be confounded by medications influencing the autonomic nervous system (e.g., sedatives, vasopressors)

Table 2 (*continued*)

Table 2 (*continued*)

Author of study	Year of study	Study population	Number of HRV parameters analysed	Relevant HRV parameters			Conclusions	Limitations
				Time domain	Frequency domain	Non-linear		
Barnaby *et al*. (46)	2002	15	7		LFnu, LF/HF ratio		All patients who survived or did not require ventilatory or hemodynamic support had a normalised LF (LFnu) values greater than 0.5 or LF/HF ratios less than 1.0. LFnu correlated with increased illness severity as calculated using APACHE II (r=20.67, r^2=0.43) and SOFA (r=20.80, r^2=0.64) and accounted for 40–60% of the variance in illness severity scores in patients presenting with sepsis	Small sample size. Single-center study in the United States
Barnaby *et al*. (47)	2018	466	1		LF/HF ratio		LF/HF ratio <1 was only 34% sensitive (95% CI, 19–53%) in identifying patients who required critical care or died within 72 hours of presentation. A SOFA score of ≥3 or LF/HF ratio of <1 are insufficient predictors of morbidity and mortality in sepsis	Single-center study in the United States. Only study to define the endpoint within 72 hours of presentation
Pong *et al*. (48)	2019	364	22			DFA-α2, SD 2A	combination model incorporating best-performing clinical and one HRV parameter (SD2) performed best with a ROC curve of 0.91, compared to the NEWS (0.70), MEWS (0.61), qSOFA (0.70), SOFA (0.74), APACHE II (0.76)and MEDS (0.86) in predicting for 30-day IHM. Among the HRV parameters, DFA-α2 had the strongest predictive value as a rapid triage tool in septic patients	Single-center study in Singapore. Study limited to patients triaged to PACS 1 to 2. PACS 3 to 4 were excluded (PACS1 = critically ill, PACS2 = non-ambulant, PACS3 = ambulant, PACS4 = non-emergencies). 22.4% of septic patients were excluded due to ECG readings unsuitable for HRV analysis

HRV, heart rate variability; DFA- α 2, de-trended fluctuation analysis alpha-2; ROC, receiver operating characteristics; SDNN, standard deviation of all NN-intervals; RMSSD, square root of the mean of the sum of the squares of differences between adjacent NN intervals; TINN, baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all NN intervals; LF, low frequency; HF, high frequency; SD1/SD2, Poincare section; qSOFA, quick Sequential Organ Failure Assessment; NEWS, National Early Warning Score; MEWS, Modified Early Warning Score; APACHE, Acute Physiology And Chronic Health Evaluation; MEDS, Mortality in Emergency Department Score; PACS, patient acuity category scale.

performance (55,56). HRV remains a promising research field and there are ongoing studies that evaluate its utility as part of scoring systems (57).

Neonatal sepsis

Unlike pediatric and adult sepsis, there is still no commonly agreed definition for neonatal sepsis (58-60). Since continuous non-invasive cardiac monitoring is often standard procedure in the neonatal intensive care unit (NICU), studies have explored the use of HRV analysis as a diagnostic and prognostic tool for sepsis. Heart rate characteristic (HRC) index measures the degree of reduced variability and decelerations to determine the fold-increase in the risk of developing neonatal sepsis (61,62). The detection of sepsis by HRC index precedes clinician suspicion of sepsis (62-64). Studies have shown that HRC index monitoring in the NICU resulted in a reduction in mortality in very-low-birth-weight (VLBW) neonates, and its use as an independent tool in predicting for neonatal sepsis has been validated (62-65) (*Table 3*).

Looking at specific HRV parameters, time-domain indices such as NN50 count divided by the total number of all NN intervals (pNN50) was significantly decreased in neonates with sepsis as compared to healthy controls, while changes in frequency-domain indices such as very low frequency (VLF), LF, HF, and LF/HF ratio were statistically insignificant (66). However, another study showed that specific HRV parameters were not significantly modified following sepsis (67). As such, further studies are needed to determine the added value of HRV, and if time domain indices are truly more sensitive than frequency domain indices in predicting for neonatal sepsis.

Pediatric sepsis

HRV prediction in sepsis has been explored in the adults and neonates, but data on infants and children beyond the first month of life is very limited. An old PICU study of children with critical illness and injury demonstrated that HRV trends correlate with severity of illness and may have important clinical implications, but did not focus specifically on sepsis (28). ANS dysfunction in pediatric septic shock has been successfully demonstrated with HRV, but this has not translated into the use of HRV to guide clinical practice (68). In this small study of 7 children with septic shock, 6 children showed changes in the low/high frequency ratio and the authors postulate added value in using loss of HRV and complexity in monitoring these ill children (68). In another study of 22 children with known cardiovascular diseases, HRV changes may precede clinical diagnosis of sepsis by up to 24 hours (69).

Given the potential application demonstrated in adult and neonatal patients with sepsis, we postulate that HRV use can be expanded in the pediatric population. For example, HRV analysis can be investigated as a potential tool to identify septic children in the pediatric ED. Higher frequency data collection would allow the patient's evolving clinical status to be more accurately captured (70). If proven to discriminate between children with sepsis and those without, it has the potential to add to the ED physician's armamentarium on which child should have early cultures and urgent antibiotic administration, thus guiding resource utilisation.

Continuous HRV analysis, similar to those performed in the NICU, could also be explored in the PICU. Similar to the NICU septic population, a reduction in HRV could potentially precede clinical symptoms and signs of sepsis. New applications of HRV including predicting and prognosticating nosocomial and line-related sepsis in the critically ill PICU population should also be explored. The responsiveness of abnormal HRV parameters in successful treatment and resolving sepsis deserves further study. If promising, it may prove useful to guide clinicians in their monitoring and treatment strategy (28).

Limitations of HRV

Despite ongoing research efforts for the past century, HRV remains a relatively new concept to many. Before considering its use for pediatric sepsis, several limitations of HRV need to be taken into account. The current availability of ECG machines does not equate to the commercial availability of HRV analysis, and this may explain why HRV analysis has not been integrated into everyday use. There is often proprietary software and hardware requirements, with upfront cost barriers that need to be overcome. Training of personnel in data interpretation remains an issue, and healthcare professionals including doctors and nurses have to understand the principles of HRV analysis and how it may impact sepsis diagnosis and prognostication. In children specifically, artefacts need to be dealt with and post-processing capabilities are needed for meaningful analysis of HRV signals. In neonates, abnormal HRV can be affected by factors other than sepsis, such as gestational age and underlying medical conditions (71), and as such needs

Table 3 Studies evaluating the use of HRC index in neonatal sepsis

Author of study	Year of study	Study population	Aims of study	Results	Comments (if any)
Moorman *et al*. (62)	2011	3,003 VLBW neonates in 9 NICUs	Comparing number of days alive and ventilator-free for 120 days post-randomisation between neonates with and without HRC monitoring	2% mortality reduction rate in infants with HRC monitoring displayed (10.2% to 8.1%, P=0.04), with increased days alive and ventilator-free (95.9 days compared to 93.6 days in control subjects, P=0.08)	
Griffin *et al*. (63)	2003	633 infants in 2 NICUs, of which 270 were VLBW infants	To derive and validate multivariable statistical models involving HRC to predict for sepsis and sepsis-like illness in newborn infants	Regression models involving the use of HRC index is highly predictive for sepsis and sepsis-like illness in both NICUs (P<0.001), and added significantly to demographic information of birth weight, gestational age, and days of post-natal age (P<0.001). Regression models including HRC index performed better with a ROC curve of 0.77, as compared to 0.72 without HRC index	Reduced variability and transient decelerations precede clinical signs and symptoms of sepsis and sepsis-like illness in newborn infants
Griffin *et al.* (64)	2005	1,022 infants in 2 NICUs, of which 458 were VLBW infants	To evaluate the use of continuous HRC index monitoring as a risk index to identify infants who are at increased risk of sepsis, urinary tract infections or death in the NICU	Neonates with high-risk HRC index and abnormal laboratory test results had an 11% incidence of adverse outcomes compared with 2% in neonates with normal HRC and normal laboratory test results (P<0.001). High HRC with an abnormal laboratory test result have a 6- to 7-fold increase in relative risk compared to High HRC without abnormal laboratory test results (P<0.001)	HRC monitoring adds information to abnormal laboratory results in predicting neonatal outcomes

HRC, heart rate characteristics; NICUs, neonatal intensive care units; VLBW, very-low-birth-weight; ROC, receiver operating characteristics.

to be interpreted accordingly. Many prior studies have also excluded patients with cardiovascular diseases such as arrhythmias due to the lack of satisfactory RR intervals for analysis (36,37,42,43). This may potentially limit the generalisability to the wider population with a history of congenital and acquired cardiac disorders. The use of HRV in different settings can also result in undesirable effects on health services with an overall increase in interventions, hence impact on the wider healthcare setting must be evaluated before translation into practice (72). Most importantly, we acknowledge that the use of HRV has not been documented in pediatric sepsis, and the findings relating HRV to adult sepsis and neonatal sepsis may not apply similarly in this population. To establish definitive evidence, it is necessary to conduct similar studies in this setting.

Conclusions

When compared to traditional heart rate, HRV has been shown to value-add in the identification and prognostication of adults and neonates with sepsis. This exciting non-invasive tool could guide the recognition and management of pediatric sepsis and impact clinical practice.

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Footnote

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Supplementary

Table S1 Comparing the threshold values of tachycardia among selected examples of PEWS, international guidelines and large cross-sectional studies in the pediatric setting

Warning score	Author of study	Year of study	Study population	Age of patient	Threshold definition of tachycardia (bpm)
Bristol PEWT	Haines *et al*. (12)	2006	360 patients under 19 years old in pediatric wards	<5 years	≥150
				5–12 years	≥120
				>12 years	≥100
Melbourne Activation Criteria (MAC)	Edwards *et al*. (13)	2011	1,000 patients aged under 16 years old in pediatric wards	<12 months	>180
				1–4 years	>160
				5–12 years	>140
				>12 years	>130
PEWS score	Duncan *et al*. (14)	2006	215 patients under 18 years old in pediatric wards	<3 months	>180
				3–12 months	>170
				1–4 years	>150
				4–12 years	>130
				>12 years	>120
Modified Brighton PEWS	Skaletzky *et al*. (15)	2012	350 children under 18 years old in pediatric medical-surgical wards	<3 months	>205
				3–24 months	>190
				2–10 years	>140
				>10 years	>100
Evidence-based cross-sectional studies*	Fleming *et al*. (18)	2011	143,346 children aged under 18 years old	<1 month	>182
				1–2 months	>180
				2–3 months	>178
				3–6 months	>172
				6–9 months	>165
				9–12 months	>159
				1–2 years	>147
				2–4 years	>135
				4–6 years	>126
				6–8 years	>120
				8–10 years	>116
				10–12 years	>112
				12–14 years	>108
				14–16 years	>105
				16–18 years	>102
	O'Leary *et al.* (19)	2015	111,696 children aged under 15 years old	<3 months	>181
				3–6 months	>174
				6–9 months	>172
				10–12 months	>174
				12–18 months	>176
				18–24 months	>172
				2–3 years	>162
				3–4 years	>152
				4–6 years	>146
				6–8 years	>141
				8–12 years	>135
				12–15 years	>127
				15–16 years	>122
	Bonafide *et al*. (20)	2013	116,383 children under 18 years old	< 3 months	>186
				3–6 months	>182
				6–9 months	>178
				9–12 months	>176
				12–18 months	>173
				18–24 months	>170
				2–3 years	>167
				3–4 years	>164
				4–6 years	>161
				6–8 years	>155
				8–12 years	>147
				12–15 years	>138
				15–18 years	>132
Consensus-based international guidelines	Advanced Pediatric Life Support (APLS) (21)	2004		<1 year	>160
				1–2 years	>150
				2–5 years	>140
				5–12 years	>120
				12–18 years	>100
	Pediatric Advanced Life Support (PALS) (22)	2006		<6 months	>200
				6–24 months	>190
				2–10 years	>140
				10–18 years	>100

*, data in the last row mean suggested cut-off points of tachycardia. PEWS, Pediatric Early Warning Systems; bpm, beats per minute.