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REVIEW ARTICLE
Hemodynamic dysfunction in neonatal sepsis

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Cardiovascular disturbances are a frequent occurrence in neonatal sepsis. Preterm and term infants are particularly vulnerable due to the unique features of their cardiovascular function and reserve, compared to older children and adults. The clinical manifestations of neonatal sepsis are a product of the variable inflammatory pathways involved (warm vs. cold shock physiology), developmental state of the cardiovascular system, and hormonal responses. Targeted neonatal echocardiography has played an important role in advancing our knowledge, may help delineate specific hemodynamic phenotypes in real-time, and supports an individualized physiology-based management of sepsis-associated cardiovascular dysfunction.

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IMPACT: Cardiovascular dysfunction is a common sequela of sepsis. This review aims to highlight the pathophysiological mechanisms involved in hemodynamic disturbance in neonatal sepsis, provide insights from targeted neonatal echocardiography-based clinical studies, and suggest its potential incorporation in day-to-day management.

Sepsis is one of the most commonly encountered pathologies in the neonatal intensive care unit (NICU) and is associated with significant morbidity and mortality.[1] Many infants with sepsis develop cardiovascular instability; preterm infants are particularly vulnerable due to the unique features of their cardiovascular function and reserve. The aim of this review is to highlight the pathophysiological mechanisms involved in a hemodynamic disturbance in neonatal sepsis, provide insights gained from targeted neonatal echocardiography (TNE)-based clinical studies, and suggest its potential incorporation in day-to-day management.

CARDIOVASCULAR FUNCTION IN SEPSIS
Characterization of sepsis-related cardiovascular dysfunction has been traditionally based on the clinical patterns identified by bedside physical examination, typically dichotomized as warm and cold shock physiology.[2] Warm shock is defined by significant vasodilation leading to low systemic vascular resistance (SVR), producing hypotension, brisk capillary refill time (CRT), bounding peripheral pulses, and flushed skin. Conversely, cold shock is a vasoconstrictive state, causing cold or pale extremities, delayed CRT, and weak peripheral pulses. Initially, blood pressure (BP) may be falsely reassuring as it remains elevated despite inadequate cardiac output due to marked peripheral vasoconstriction.[3] Hypotension is often a late finding in cold shock and is a consequence of the significant reduction of left ventricular systolic performance from prolonged exposure to high afterload.

Changes in SVR associated with sepsis can have significant implications on cardiac mechanics. Peripheral vasodilation may result in lower systemic venous return and decreased right-heart preload. Tachycardia may compensate to maintain cardiac output, although neither adequately nor indefinitely. On TNE, although this generates a hyperdynamic cardiac profile, this partially compensated vasodilatory state can ultimately result in below normal range ventricular outputs, particularly in preterm neonates. Further, diminished venous return and left-heart preload may reduce left ventricular systolic performance via Frank–Starling mechanisms,[4] potentially exacerbating the direct adverse impact of inflammation on myocardial contractility.[5] These insults on systolic function elevate left ventricular end-diastolic pressure, further compromising its filling and may even negatively impact the right ventricle through ventricular interdependence.[6] Right ventricular filling and function may also be directly compromised in the setting of elevated pulmonary vascular resistance (PVR) states that are not infrequently encountered in neonatal sepsis, such as acute pulmonary hypertension[7] and hypoxic pulmonary vasoconstriction[8] (a ventilation–perfusion sparing arteriolar response to diminished alveolar oxygen content).

Likewise, elevated SVR associated with cold shock physiology can have major adverse effects on the myocardium. Neonatal heart, even more so for preterm neonates, is known to be highly intolerant to acute increases in afterload,[9] which can result in left ventricular systolic dysfunction, low stroke volume, and a subsequent increase in both end-systolic and end-diastolic pressures, compromising filling. Initially, the left ventricle may adapt, at least partially, in order to maintain its stroke volume by increasing inherent contractile force, tachycardia, and dilatation. However, both the contractile reserve and the ability to increase stroke volume by dilatation are limited in preterm heart,[10] making these patients more vulnerable to ventricular dysfunction, low stroke volume, and, consequently, worsening hypotension and shock.

Hence, the unique clinical phenotype in neonatal sepsis is the culmination of the type of shock physiology and may evolve over the course of an illness. Understanding the specific underlying

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mechanisms at play is key to tailoring therapeutic interventions and providing individualized management, necessitating frequent re-evaluation and readjustment of management strategies to the changing clinical picture.

Challenges in clinical assessment and limitations of BP measurements

Although the dichotomous presentation has been useful for the establishment of clinical practice guidelines, distinguishing between "warm shock" and "cold shock" based on clinical assessment alone may be prone to error.[11] Central CRT has been inconsistently shown to correlate with systemic blood flow,[12–14] while peripheral CRT is not a reliable index for assessing the hemodynamic status of neonates.[15–17] BP measurements, although often the primary criteria used by clinicians to diagnose shock and initiate treatments, can be particularly difficult in neonates. This relates to both the lack of established technical standards and known unreliability of selecting appropriate cuff sizes,[18] as well as the lack of research to inform robust interpretation. Although a number of studies have reported on normative values[19–21] (albeit mostly using data from older cohorts during the initial days after birth, prior to widespread integration of strategies such as delayed cord clamping and antenatal corticosteroids), data regarding specific thresholds to define "hypotension" beyond the transitional period associated with adverse clinical outcomes, or in acute conditions such as sepsis remain limited.[22] Further, noninvasive BP recordings are known to be higher in preterm neonates compared to invasive readings.[23,24] In practice, mean BP below corrected gestational age, referred to as the British Association of Perinatal Medicine rule,[25] is often used by clinicians to guide interventions, presumably driven by lack of other data and ease of use. However, this consensus-driven rule was suggested in the context of transitional hypotension in extremely preterm neonates, and its extrapolation to acute complications later in the postnatal course may be ill-informed and cannot be recommended. Given these challenges, pending further research, a more thoughtful and thorough appraisal of the circulatory system is warranted to find the balance between avoiding both unnecessary and indiscriminate use of drugs and delaying treatment for neonates in circulatory compromise. One potential interim clinical strategy may be to compare BP recordings during the sepsis episode to the patient's own pre-illness baseline values and corroborate changes with any evidence of end-organ dysfunction, in order to detect deviations that may be clinically relevant for individual patients.

MECHANISMS OF CARDIOVASCULAR DYSFUNCTION
Inflammation
Inflammatory pathways activated in sepsis may directly impact the vascular tone and cardiac function, and play a critical role in defining the clinical hemodynamic presentation. The host response to sepsis induces immune system activation and an endothelial response. In its native state, the endothelium and its components have multiple roles including barrier function and vasomotor regulation.[26] The release of inflammatory mediators in sepsis can compromise endothelial wall integrity through the destruction of gap junctions;[26] subsequent endothelial leakiness causes fluid shifts to extravascular spaces, lowering circulating blood volume, and subsequently cardiac preload. Inflammation can also compromise endothelial glycocalyx, releasing nitric oxide (NO) and endothelin, two predominant mediators of vascular tone, resulting in alterations in blood flow to organs.[27] In adults with sepsis, NO in its inducible form plays a role in arteriolar vasodilatation and microvascular dysfunction,[28–30] and activation of NO signaling pathways has been found to decrease cardiac myocyte responsiveness to beta-adrenergic agonists,[31] modulate pulmonary vascular tone,[32] and cause vascular hyporeactivity.[33]

Elevated levels of endothelin, a potent vasoconstrictor, have been correlated with illness severity and myocardial dysfunction in sepsis.[34–36] Among neonates, bacteremic infants have also been found to have higher levels of both NO and endothelin compared to noninfected patients,[37,38] indicating a potentially similar pathophysiological role. The relative expression of these mediators may dictate the vasoactive phenotype and its severity in patients with sepsis. Further, when pro-inflammatory pathways in sepsis are not appropriately counteracted by anti-inflammatory mechanisms, dysregulated inflammation or systemic inflammatory response syndrome (SIRS) may occur, causing additional compromise to microcirculatory perfusion and oxygen delivery.[39,40] Although neonates generate a relatively lower amount of inflammatory cytokines compared to adults,[41] SIRS may complicate the clinical course for many patients. In addition, inflammation can directly impact the heart. In animal models of sepsis, various cytokines have been shown to depress cardiac contractility,[42] alter coronary arterial autoregulation,[43] and trigger excessive interstitial infiltration of inflammatory mediators in the myocardium.[44] While specific neonatal studies are lacking, sepsis-induced myocardial dysfunction, and cardiomyopathy, directly mediated by inflammatory mediators, are well-established.

Hormonal influences
In addition to immune activation, sepsis also triggers neuroendocrine responses, leading to the release of catecholamines and the recruitment of additional hormonal pathways. Vasopressin and cortisol are the most studied adjunctive hormones that are thought to play important hemodynamic roles in sepsis. Although high-quality studies examining the use of exogenous catecholamines, vasopressin, and corticosteroids in neonatal sepsis are lacking, these agents are frequently used in the clinical setting for hypotension in sepsis,[45–47] presumably driven by pathophysiological considerations and extrapolation of evidence from adult critical care.

Catecholamines. The release of endogenous catecholamines is induced by bacteria or bacterial products such as endotoxins, in part due to stimulation of pro-inflammatory pathways.[48] In turn, catecholamines exert anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines and augmenting the release of anti-inflammatory cytokines. The catecholamine effect is predominantly beta-adrenergic, although some alpha-adrenergic activation can be seen.[49]

Vasopressin. Vasopressin or antidiuretic hormone, responsible for regulating circulating volume and osmolality under physiological conditions, appears to play an important role in severe sepsis and catecholamine-unresponsive sepsis-induced hypotension among older patients.[50] It acts via V1a receptors to induce vascular smooth muscle vasoconstriction, providing a catecholamine receptor-independent pathway to modulate vasodilation.[51] In sepsis, circulating vasopressin levels are described to be abnormally low,[52] and its stores deplete quicker in shock due to sepsis vs. non-septic etiologies such as cardiogenic shock.[53,54] While there are no large trials, in adult critical care, vasopressin is being increasingly used as an adjunctive therapy for catecholamine-unresponsive hypotension from sepsis.[55]

Cortisol. Cortisol plays many roles in maintaining cardiovascular stability, including regulating transmembrane calcium homeostasis, augmenting beta-receptor frequency and limiting their degradation, and increasing adrenergic receptor sensitivity to circulating catecholamines.[56] Cortisol is critical to maintaining homeostasis especially in response to physiologic stress; preterm infants, however, are thought to have relative adrenal insufficiency related to an immature hypothalamic–pituitary axis as well as a limited ability of the adrenal gland for *de novo* cortisol synthesis.[57] Preterm infants needing vasopressor therapies demonstrate lower
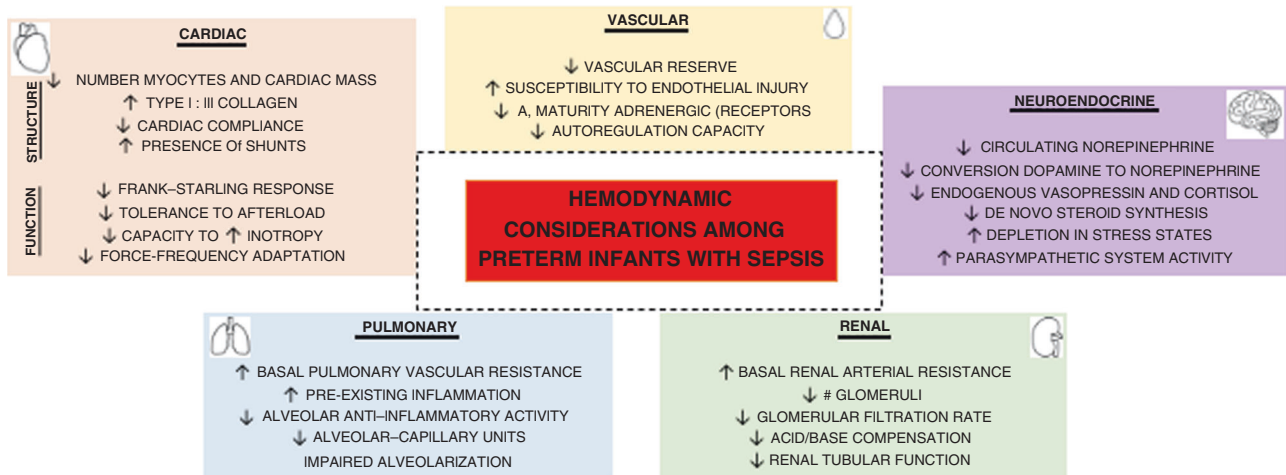
Fig. 1 Hemodynamic considerations among preterm infants with sepsis. Potential factors that may contribute to the unique hemodynamic phenotype during sepsis among preterm infants based on affected organ.

basal and stimulated cortisol levels,[58,59] which may be due to low conversion of cortisol precursors.[60] In addition, glucocorticoids are thought to have an essential function in maintaining vascular wall integrity, which may have a role in regulating sepsis-related endothelial destruction and related capillary leak.[61]

EXTRACARDIAC PHYSIOLOGIC CONTRIBUTIONS TO HEMODYNAMIC INSTABILITY
Renal
Adequate renal function is critical to managing shifts in fluid balance that can occur during sepsis from factors such as volume resuscitation, cardiac pump function, and "third spacing" due to loss of endothelial integrity. In sepsis, renal injury can occur through both altered perfusion and direct tubular injury. Studies in adults have demonstrated that despite a hyperdynamic state with globally increased cardiac output, sepsis is often associated with loss of renal autoregulation.[62] Microcirculatory changes within the renal cortex or medulla can also occur in sepsis, independent of normal or even increased renal blood flow,[63] largely stemming from the inflammation-mediated local release of excessive NO.[26] Renal damage through tubular injury is thought to be related to pro-inflammatory cytokines filtered through the glomerulus, directly impacting the proximal tubules.[64,65] Given the challenges and often lack of feasibility of renal replacement therapy in neonatal patients, clinicians must remain vigilant in anticipating the potential consequences of associated renal failure and avoid, as much as possible, fluid overload from overzealous use of volume resuscitation. Mortality in neonates who develop renal failure in sepsis has recently been noted to be higher than in those without renal failure,[66] although exact mechanisms and therapeutic targets remain to be elucidated.

Respiratory
Respiratory failure is a common manifestation of neonatal sepsis and may originate from either ventilation–perfusion mismatch from acute pulmonary hypertension, or impaired oxygen transport at the alveolar or interstitial level, referred to its most severe form as acute respiratory distress syndrome (ARDS). The distinction is crucial to optimizing management; strategies to lower PVR are the mainstay for an acute pulmonary hypertension crisis, while for ARDS, typical strategies include an exogenous surfactant, prone positioning, and trial of conventional ventilation.[67] Sepsis-related acute pulmonary hypertension is thought to result from the excessive production of vasoconstrictor mediators such as endothelins.[68,69] Early use of echocardiography for neonates with sepsis-associated hypoxic

respiratory failure to assess the presence of pulmonary hypertension may aid timely diagnosis and appropriate titration of therapies. Pathophysiologically, ARDS results from pro-inflammatory plasma proteins leaking in the alveolar space causing damage to the surfactant biofilm. Lysis of the surfactant phospholipid releases free fatty acids, triggering the release of more inflammatory mediators.[70] In adult critical care, ARDS is well studied with established diagnostic criteria, manifesting as significant respiratory failure with new hazy infiltrates on chest x-ray.[71] In neonatal medicine, however, ARDS is generally underappreciated and likely underdiagnosed, perhaps because of a lack of established diagnostic criteria, difficulty in clinically distinguishing from acute pulmonary hypertension, and a decreased awareness among neonatal clinicians of ARDS as a potential etiology of severe hypoxic respiratory failure. Recently, an international group published a consensus-based operational definition for neonatal ARDS,[71] although its clinical validity, utilization, and impact need further evaluation. It is essential that clinicians looking after neonates with sepsis maintain a high index of suspicion for ARDS.

ADDITIONAL CARDIOVASCULAR CONSIDERATIONS IN PREMATURE NEONATES WITH SEPSIS
In addition to the organ-specific physiological factors highlighted above, there are developmentally regulated cardiovascular structural and functional considerations that may govern the overall hemodynamic phenotype and ability to accommodate altered physiologic states in premature neonates (Fig. 1). *Structurally*, the immature heart has less lower mass, fewer and less organized myofibrils, fewer mitochondria (amounting to lower inherent inotropy and contractile reserve), fewer L-type calcium channels, and shallower T-tubules, resulting in decreased ability to facilitate the release of calcium from sarcoplasmic stores (amounting to lower ability to generate contractile force and active relaxation), higher overall collagen content as well as a higher ratio of collagen rigidity-increasing type I to elasticity-increasing type III (amounting to lower compliance and higher stiffness), and less adrenergic innervation and adrenoreceptor density.[72–76] *Functionally*, these anatomic differences translate to lower functional reserve in response to altered loading conditions and stresses,[77] lower diastolic performance, less ability to increase stroke volume in response to increases in preload, and a greater tendency for systolic dysfunction and lower stroke volume in face of acute increases in afterload.[78–80]

While individual variations may occur, the predominant physiological response to sepsis in the vascular system also appears to be developmentally regulated. In adult patients, the predominant

Table 1. Echocardiography-based studies in neonatal sepsis.

First author	Study setting	Population	Gestational age (weeks)	Key findings	Interpretation
de Waal and Evans[90]	The Netherlands August 2008–September 2009	20 infants, <34 w GA with suspected infection >72 h of life, with two signs of cardiovascular compromise	Median GA 27 (range 25–32)	Mean (SD) RVO 555 (133) and LVO 441 (164) mL/kg/min Mean (SD) calculated SVR 0.08 (0.04) mm Hg/mL/kg/min Decrease in RVO or LVO > 50% was associated with mortality	Elevated cardiac outputs and low SVR consistent with warm shock physiology Significant drop in cardiac outputs may correlate with outcomes
Abdel-Hady et al.[91]	Egypt October 2009–August 2010	20 term infants with sepsis; 20 controls	Mean GA sepsis 38.6 ± 1.3 vs. controls 38.7 ± 1.7	MPI significantly higher in septic (RV: 0.51 ± 0.09; LV: 0.56 ± 0.07) compared to controls (RV: 0.28 ± 0.05; LV: 0.39 ± 0.04) ($p < 0.0001$ for all). Tricuspid and mitral peak annular systolic velocities were significantly lower in septic neonates (TV: 5.55 ± 0.66; MV: 4.35 ± 0.68) vs. controls (TV: 6.69 ± 0.87; MV: 6.89 ± 0.94) cm/s ($p < 0.0001$). LV, but not RV, MPI lower in survivors than nonsurvivors	Global cardiac function reduced in sepsis. LV MPI may correlate with outcomes
Tomerak et al.[92]	Egypt May 2007–January 2008	30 infants with sepsis; 30 controls Divided into four study groups	Septic: Term 38.1 ± 0.9, Preterm 33.4 ± 2.7 Controls: Term 38 ± 0.7, Preterm 35.1 ± 0.8	Lower E/A in term sepsis (0.92 ± 0.69) vs. controls (1.24 ± 0.46) and preterm sepsis (0.75 ± 0.35) vs. controls (1.34 ± 0.55) ($p = 0.014$) Lower MPI in survivors (0.28 ± 0.22) vs. nonsurvivors (0.60 ± 0.23) ($p < 0.01$)	Left ventricular diastolic function reduced in sepsis. MPI may correlate with outcomes
Saini et al.[93]	India March 2010–August 2012	52 inborn infants with septic shock; 52 matched controls	Mean GA septic shock 31.1 ± 2.8 vs. controls 31.2 ± 2.3	LVO higher in sepsis (305 [204, 393]) vs. controls (233 [204, 302]) mL/kg/min ($p < 0.001$) No difference in ejection fraction (55 ± 12 vs. 55 ± 5 %) ($p = 0.54$) More infants with septic shock had a PDA (60% vs. 23%, $p = 0.005$) Significant increase in RVO pre-vasopressor (376 [286, 468]) vs. post-vasopressor (407 [323, 538]) mL/kg/min ($p = 0.018$)	Elevated LVO and vasopressor-responsive RVO consistent with warm shock physiology, although higher LVO may reflect ductal flow in this study as no difference in EF
Ramadhina et al.[94]	Indonesia June 1–August 31, 2013	30 preterm infants with sepsis (with or without positive blood cultures)	Mean GA 31.5 ± 2.2	Mean LV MPI (SD) 0.28 ± 0.07 Median RV MPI (range) 0.25 (0.17–0.59) Moderate correlation of LV MPI and high-sensitivity cardiac troponin ($r = 0.58$, $p < 0.01$)	Cardiac troponin levels may reflect myocardial injury in sepsis
Awany et al.[95]	Egypt January 2014–June 2015	40 term neonates with culture-positive sepsis; 40 controls	Sepsis mean GA 38.0 ± 0.8; controls 37.9 ± 0.8	Elevated LV and RV MPI in sepsis (LV: 0.47 ± 0.05; RV: 0.44 ± 0.55) vs. controls (LV: 0.38 ± 0.06; RV: 0.36 ± 0.06) Elevated peak systolic pressure in sepsis (38.5 ± 5.0) vs. controls (30.5 ± 4.0) Lower E/A' in sepsis vs. controls (mitral: 0.50 ± 0.14 vs. 1.10 ± 0.17;	Global cardiac function reduced in sepsis. Infants with sepsis may be at increased risk for acute pulmonary hypertension

Table 1. continued

First author	Study setting	Population	Gestational age (weeks)	Key findings	Interpretation
Alzahrani[96]	Saudi Arabia	30 term neonates with sepsis; 30 controls	Full-term	tricuspid: 0.84 ± 0.05 vs. 1.21 ± 0.04) All $p < 0.01$ EF lower in sepsis (65.74 ± 0.64) vs. controls (71.11 ± 0.79)% ($p < 0.01$) FS lower in sepsis (30.14 ± 0.59) vs. controls (33.90 ± 0.60)% ($p < 0.01$)	Left ventricular systolic dysfunction may be a feature of sepsis
Deshpande et al.[97]	India March 2015–November 2015	31 infants with positive blood cultures	67.7% preterm	Mean RVO 313 ± 11.4 and LVO 347 ± 139.9 ml/kg/min, respectively Higher RVO (338 vs. 225, $p = 0.014$) and LVO (378 vs. 241, $p = 0.02$) seen in gram-negative vs. gram-positive infections	Elevated cardiac outputs consistent with warm shock physiology Gram negative sepsis may be associated with a low systematic vascular resistance state
Fahmey et al.[98]	Egypt Feb–Nov 2017	50 neonates with sepsis (28 EOS, 22 LOS), 25 controls	Sepsis mean GA 36.1 ± 2.9; controls 36.7 ± 0.9	MV E/A ratio lower in sepsis (0.87 ± 0.19) vs. controls (1.08 ± 0.19) ($p = 0.05$) Pulmonary systolic pressure (mm Hg) higher in sepsis (32.1 ± 11.9) vs. controls (24.5 ± 5.5) ($p < 0.001$) Survivors had higher LVFS compared to nonsurvivors (38.0 ± 6.6 vs. 33.8 ± 9.3, $p = 0.04$).	Left ventricular diastolic function may be a feature of sepsis Infants with sepsis may be at increased risk for acute pulmonary hypertension
Deshpande et al.[99]	India April–October 2019	33 preterm and term infants with culture-positive late-onset sepsis; 33 controls	27.3% <32 in both groups	Pulmonary artery systolic pressure higher in sepsis (35.3 ± 10.1) vs. controls (12.6 ± 3.9) mm Hg ($p < 0.01$)	Infants with sepsis may be at increased risk for acute pulmonary hypertension
Saini et al.[100]	India August 2012–December 2019	23 infants with septic shock; 23 matched controls	Mean GA septic shock 30.9 ± 3.3 vs. controls 30.3 ± 2.9	IVC-collapsibility index higher in septic shock (53 [21, 100]) vs. controls (20 [15, 24])% ($p = 0.01$)	Fluid-responsive low preload state in sepsis
Yengkhom et al.[101]	India March 2017–May 2018	67 infants with culture-positive late-onset sepsis	Mean GA 33.3 ± 3.56	Increased cardiac output in 40% of patients Increased pulmonary pressures in 25% patients	Elevated cardiac output consistent with warm shock physiology Infants with sepsis may be at increased risk for acute pulmonary hypertension

All studies are prospective cohort studies.
GA gestational age, SD standard deviation, IVC inferior vena cava, RV right ventricular, RVO right ventricular output, LV left ventricular, LVO left ventricular output, TV tricuspid valve, MV mitral valve, EF ejection fraction, FS fractional shortening, MPI myocardial performance index, EOS early-onset sepsis, LOS late-onset sepsis.

physiology is known to be that of warm shock,[81] whereas in children, sepsis tends to produce primarily cold shock physiology.[82,83] Physiological studies in preterm infants, similar to adults, have demonstrated warm shock physiology to be the predominant phenotype.[39,84] This is postulated to be due to an impaired ability to regulate vascular tone during shock,[39] in part driven by an inherent imbalance of the autonomic nervous system characterized by a relatively higher parasympathetic drive.[85] Relative adrenal insufficiency, by decreasing SVR, may also be a contributing factor in preterm infants.[86] Further, preterm neonates have a baseline elevated PVR by virtue of a lower capacity vascular bed, which, in combination with pre-existing lung disease often seen in these patients, may place them at higher risk of pulmonary vascular complications such as acute pulmonary hypertension and pulmonary edema.[87]

TNE IN NEONATAL SEPSIS

TNE or neonatologist-performed echocardiography refers to the bedside use of functional echocardiography by neonatologists extensively trained in cardiovascular physiology and hemodynamic assessment of critically sick neonates.[88] Clinical integration of the comprehensive hemodynamic data obtained through TNE allows the definition of underlying cardiovascular physiology in real-time, titration of therapeutic interventions and dose-targeting, and sequential assessments to monitor disease progression and treatment response. Recently, a large number of NICUs across the globe have adopted an in-house TNE program, allowing for its increasing incorporation in day-to-day assessment and management of hemodynamic complications.[89] The widespread availability of appropriate equipment and development of local expertise have also opened the doors for hemodynamic researchers to undertake physiological explorations in this vulnerable and high-risk patient population.

Although large definitive TNE-based studies are still needed, over the past 10 years, several physiological studies have been published providing important clues to help advance our understanding of hemodynamic complications of neonatal sepsis.[90–101] The salient features of these TNE-based studies are summarized in Table 1. In summary, these studies have consistently demonstrated that the predominant phenotype associated with sepsis in neonates is of warm shock physiology, characterized by lower venous return (higher inferior vena cava collapsibility), lower calculated SVR, and higher cardiac outputs compared to controls or published normative values.[90,93,97,100,101] Septic patients also consistently demonstrate inferior diastolic and global cardiac performance (myocardial performance index or Tei index) for both the right and left ventricle.[91,92,95,96,98] The findings in relation to systolic performance are more equivocal. One study reported mildly lower conventional markers of systolic function (ejection fraction, fractional shortening) during sepsis vs. controls, albeit still within normal range;[96] another found no difference.[93] Systolic function using tissue Doppler velocities in one study found lower velocities in sepsis;[95] however, this marker is highly load-dependent and lower velocity may be a reflection of lower preload instead of contractility. Myocardial deformation parameters such as strain and strain rate have not been assessed during sepsis in neonates. Similarly, while acute pulmonary hypertension has been reported as a complication of neonatal sepsis,[98,99,102,103] its systematic evaluation using echocardiography outside of the transitional period and the impact of pulmonary vasodilator therapies have not been described. The few studies reporting on pulmonary arterial pressures have found a significant but mild increase in TNE-measured pulmonary arterial pressures during sepsis compared to controls; however, the actual pressures were still too low to be clinically relevant.[95,98,99] Echocardiographic findings in patients presenting with hypoxic respiratory failure in sepsis are not described. Few small studies have also examined the prognostic significance of TNE-derived variables. Although

these data at present are weak and not definitive, they suggest that some TNE variables may have prognostic value for clinical outcomes. Sepsis survivors were found to have a relatively lower myocardial performance index (better global performance) and slightly higher left ventricular fractional shortening (systolic function).[91,92,98] Ultimately, systematic, prospective, and adequately powered investigations are needed to establish the prognostic value of TNE.

MANAGEMENT OF HEMODYNAMIC DYSFUNCTION IN NEONATES WITH SEPSIS AND ROLE FOR TNE
General principles and monitoring

Early and adequate hemodynamic stabilization is a key component of critical care in sepsis. Prompt identification of patients with progression of sepsis severity may be accomplished through frequent clinical assessments and monitoring of changes to physiologic indices (heart rate, BP, urine output, CRT, and neurologic status) and biochemical variables (blood gas, lactate, electrolytes, and creatinine). Continuous physiologic monitoring of invasively acquired resuscitative endpoints such as central venous oxygen saturation is typically not feasible in neonates; clinicians are therefore reliant on serial bedside assessments and intermittent blood sampling to monitor disease progression and response to therapeutic interventions. Clues to the underlying initial hemodynamic physiology may be derived from the type of hypotension exhibited. Diastolic BP is more reflective of SVR;[104] therefore, hypotension driven mainly by lower diastolic BP may indicate a vasodilatory state. On the other hand, an exclusively lower systolic BP may be more indicative of low left ventricular output.[105] In many cases, both diastolic and systolic BPs may be low. Careful appraisal of the BP component that decreased first may prove to be helpful. In our experience, particularly in preterm neonates with warm shock, hypotension often starts as low diastolic BP and progresses to both low diastolic and systolic BP. These cases may represent initial cardiac compensation to maintain stroke volume (normal initial systolic BP), which, after a variable time-period, fails to keep up with ongoing decreases in preload, resulting in a drop in cardiac output and ultimately lowering of both BP components. The primary physiology in these cases is of low SVR.

Although BP is the most commonly used bedside hemodynamic variable in this population, it alone may not adequately reflect organ perfusion and must be interpreted in the context of other markers of organ function obtained through physical examination and laboratory investigations. Invasive BP monitoring is frequently not feasible in preterm infants due to technical challenges. Regular cycling of noninvasive BP is often the only option, although it may overestimate BP.[23,24] Near-infrared spectroscopy (NIRS) and continuous cardiac output monitoring are promising modalities that may provide valuable data on tissue perfusion and changes in pump function; however, their routine use at present is limited by resource availability and lack of operational thresholds to direct interventions. At this time, evaluation of physiologic changes in sepsis remains primarily through serial patient assessments. Clinicians must stay vigilant and practice a high index of suspicion recognizing the limitations and nonspecific nature of physical exam findings in this patient population, which may miss key nuances in identifying underlying cardiovascular physiology.

Choice of vasoactive medications

When hypotension or deceased organ perfusion is noted, strategies to improve systemic blood flow must be considered. Initial resuscitation is typically through fluid administration, although this must be done judiciously, given preterm infants' decreased ability to adjust to sudden changes in loading conditions. If low organ perfusion persists, vasoactive medications are initiated. Given the predominant phenotype of warm shock physiology, vasopressors are usually started first-line; although no strong evidence currently exists to guide primary drug choice

Table 2. Overview of approach to targeted neonatal echocardiography assessment of hemodynamics in neonates with sepsis.

Key echocardiographic markers	Significance	Potential considerations for clinical management of associated hypotension
Left ventricular output	Reflects systemic blood flow in the absence of ductal shunt	*Elevated*
		Hyperdynamic state, suggestive of warm shock physiology
		• Fluid resuscitation
		• Vasopressor
		Reduced
		If in the presence of normal or elevated systolic function, indicates low preload (typically with low end-diastolic volume):
		• Fluid resuscitation
		• Vasopressor
		If in the context of reduced systolic function (e.g., direct effects of sepsis):
		• Inotrope
		• Avoid afterload increasing agents
Right ventricular output	Reflects systemic venous return in the absence of septal shunts	*Reduced*
		If in the presence of normal or elevated systolic function, indicates low preload (typically with low end-diastolic volume):
		• Fluid resuscitation
		• Vasopressor
		If in the context of pulmonary hypertension and reduced systolic function:
		• Pulmonary vasodilator
		• Optimization of ventilator management
		• Inotrope
		If in the context of reduced systolic function without evidence of pulmonary hypertension (e.g., direct):
		• Inotrope
		• Avoid afterload increasing agents
PDA flow directionality PDA Doppler	Relation between pulmonary and systemic pressures	Right to left shunting indicates supra-systemic pulmonary arterial pressures (acute pulmonary hypertension and/or systemic hypotension from warm shock). *Note*: in the presence of LV dysfunction, right to left PDA shunt may be critical to providing systemic blood flow; in the presence of RV dysfunction, it may aid offloading and protecting the right ventricle
		• Avoid therapies for ductal closure until the reassessment of PDA after acute illness
		• Pulmonary vasodilatory therapies if concomitant hypoxic respiratory failure
		• Inotropes to manage cardiac dysfunction if clinical evidence of shock/hypotension
Tricuspid regurgitation peak velocity Right ventricular systolic time intervals (RVET, PAAT) Intraventricular septum configuration	Assessment of pulmonary pressures	Acute pulmonary hypertension can occur as a complication of sepsis
		• Strategies to lower pulmonary vascular resistance
		• Consider ARDS as a potential etiology if oxygenation failure without acute pulmonary hypertension on echocardiography
Qualitative assessment Ejection fraction Fractional shortening Tissue Doppler peak systolic velocity (s′)	Evaluation of left ventricular function	*Elevated*
		Hyperdynamic state, consistent with warm shock physiology
		• Fluid resuscitation
		• Vasopressor
		Reduced
		Cardiac dysfunction is either due to direct effects of sepsis or adverse loading conditions (low preload [indicated by low end-diastolic volumes] or high afterload [high blood pressure, chamber dilatation])
		• If blood pressure low: inotropes
		• If blood pressure is normal or high: inodilators such as milrinone

Table 2. continued

Key echocardiographic markers	Significance	Potential considerations for clinical management of associated hypotension
Qualitative assessment Fractional area change Tricuspid annual plane systolic excursion	Evaluation of right ventricular function	*Reduced*
		If in the presence of pulmonary hypertension:
		• Pulmonary vasodilator
		• Optimization of ventilator management
		If in the context of reduced systolic function (e.g., direct effects of sepsis):
		• Inotrope

LV left ventricular, *RV* right ventricular, *PDA* patent ductus arteriosus, *RVET* right ventricular ejection time, *PAAT* pulmonary artery acceleration time, *EF* ejection fraction, *FS* fractional shortening, *FAC* fractional area change, *TAPSE* tricuspid annual plane systolic excursion, *ARDS* acute respiratory distress syndrome.

among infants. Dopamine is the most commonly used vasopressor in the NICU and has been shown to be safe and effective in increasing BP during transitional hypotension;[106] however, its use has not been studied rigorously in late-onset sepsis. Among adults, recent meta-analyses have shown that dopamine was associated with higher mortality and an increased frequency of arrhythmias compared to norepinephrine.[107,108] Clinical practice guidelines for sepsis management in adults, the Surviving Sepsis guidelines, have integrated these findings; norepinephrine is now recommended as the first-line vasopressor for sepsis-induced hypotension in adults (strong recommendation, moderate quality of evidence).[109] Norepinephrine use has been shown to increase BP, cardiac output, and regional blood flow,[110–112] and may also improve outcomes among adult patients with septic shock.[113] Similarly, the pediatric iteration of the Surviving Sepsis guidelines recommends norepinephrine, rather than dopamine, as a first-line vasopressor (weak recommendation, very low quality of evidence).[114] Although this guideline does include neonates, the recommendations are limited to term infants with sepsis in the transitional period. Small cohort studies have found that norepinephrine may have a role in neonatal septic shock.[115,116] Dopamine has been compared with epinephrine in one trial of 40 neonates with fluid-refractory septic shock, finding a similar rate of shock reversal.[117] In this study, among infants <30 6/7 weeks gestation, hemodynamic stability was more frequently seen in the epinephrine group, which may reflect preterm infants' postulated diminished ability to convert dopamine to epinephrine, thereby losing the additional benefit of dopamine effect on non-dopaminergic receptors.[118] Presumably driven by findings in older populations, many NICUs, including ours, have changed practice to using norepinephrine as the primary vasopressor in sepsis. At present, no firm recommendations can be made for first-line therapy in neonates; early recognition and prompt evaluation of treatment efficacy in an individual patient is perhaps more important than the actual drug choice.

Particularly in catecholamine-unresponsive warm shock, alternate hormonal pathways can be considered to improve hypotension. Although vasopressin is being used increasingly in NICUs for persistent hypotension, there remains little data to guide its use,[119–121] and it cannot be recommended as primary therapy. However, vasopressin may be considered as a second-line agent in catecholamine-resistant warm shock, to target BP improvement through non-catecholamine receptor pathways. Hydrocortisone has also been found to be effective in treating refractory hypotension in preterm infants and decreasing the need for inotropic support,[122–124] although data on its use specifically in sepsis-related hypotension are lacking.

Clinical incorporation of TNE in sepsis management
The use of echocardiography to guide hemodynamic management in sepsis has been shown to be associated with improved

outcomes in adults;[125] neonatal studies are still needed. Ideally, all patients demonstrating hemodynamic compromise from sepsis would have a TNE to delineate underlying pathophysiological derangements and direct individualized therapeutic interventions. However, this has significant resource implications. Round-the-clock availability of TNE may not be feasible in most centers. Identification of the hemodynamic pattern by clinical assessment, as highlighted above, is therefore important for the timely initiation of treatment. While TNE should be obtained as early as feasible in these patients, in our opinion, an urgent evaluation should be obtained if patients demonstrate unanticipated clinical characteristics. These include clinical features suggestive of cold shock physiology (which has cardiovascular implications that may be challenging to appreciate clinically), severe hypoxic respiratory failure (which may be associated with pulmonary hypertension and can be difficult to differentiate from ARDS), and when there is a suspicion of change in underlying physiology (because of unexpected deterioration after initial stabilization or failure of expected response to initial treatments). When performed, TNE clinicians must interpret echocardiography findings in the context of the clinical picture to appropriately identify the pathophysiology and necessary therapeutic interventions. An overview of the key principles of TNE evaluation in neonatal sepsis and associated interpretation is summarized in Table 2.

In older populations, the Surviving Sepsis guidelines provide an approach to the identification and management of sepsis-related hemodynamic dysfunction.[2,109] High-quality evidence to establish similar guidelines in neonates is still needed; however, at our institution, we developed and implemented a physiology-driven consensus-based algorithm for the management of hemodynamic dysfunction in neonatal sepsis, including the role of TNE (Fig. 2). While we aspire to evaluate the impact of this policy on clinical outcomes in the future, at present this can be considered as our opinion based on physiology and currently available evidence.

FUTURE DIRECTIONS
Much of the current management in neonates with sepsis-related hemodynamic complications is driven by historical practices or extrapolation of evidence from adult studies. The developmental differences in neonates, however, have important implications, necessitating dedicated research. Studies to date have proposed a potential role for TNE, while the utility of other noninvasive modalities such as NIRS and noninvasive cardiac output monitoring remains insufficiently explored. Nonetheless, large-scale studies are still needed to establish the relevance of both static and dynamic hemodynamic variables, as well as to directly compare commonly used therapeutic options. Adequately powered clinical trials would be ideal to answer some of these outstanding questions. However, clinical trials pose significant operational challenges in neonates, highlighted by the difficulties in recruitment encountered by recent
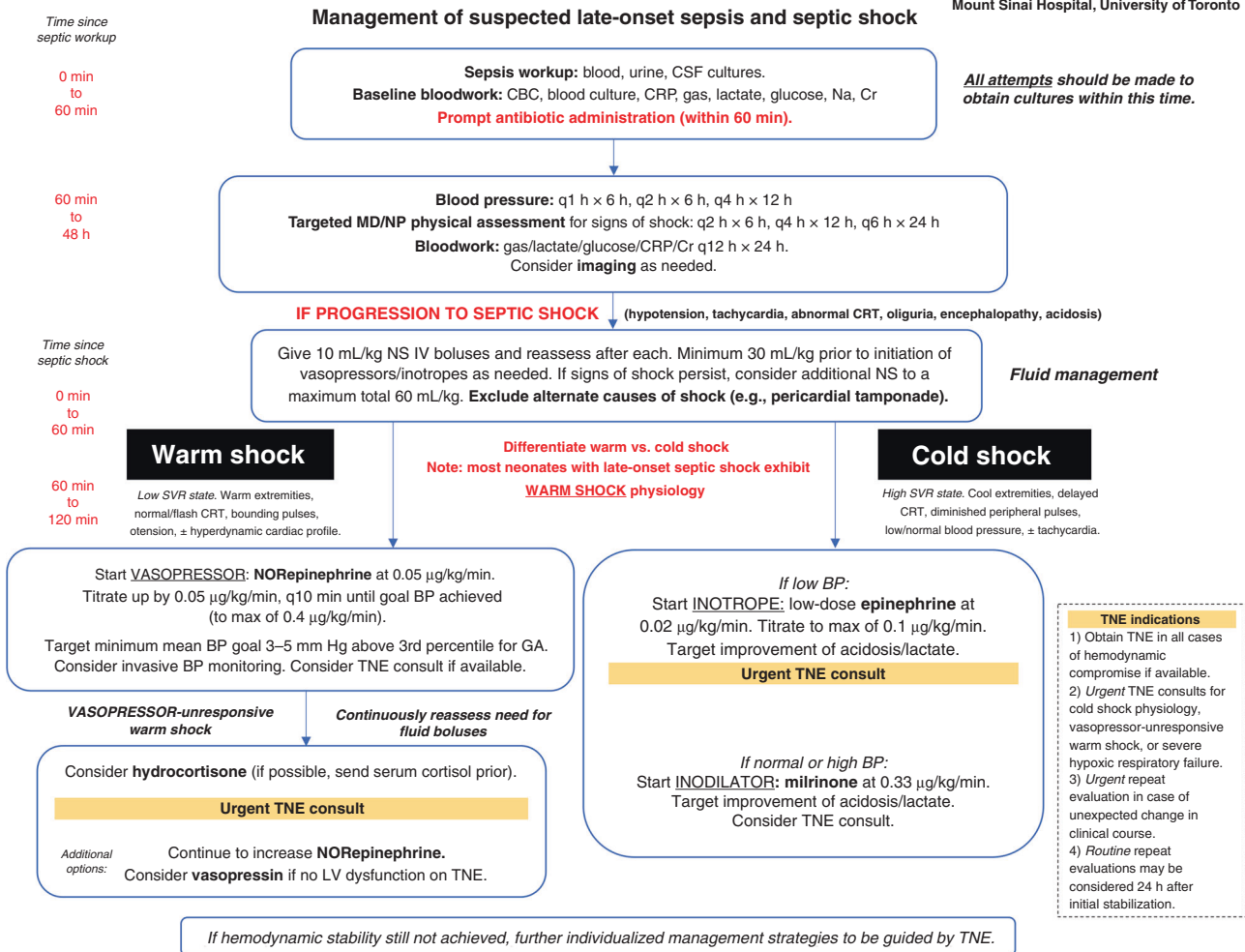
Fig. 2 Management of suspected late-onset sepsis and septic shock. This consensus-based algorithm for the physiological management of late-onset sepsis and septic shock among preterm infants was developed and implemented at Mount Sinai Hospital, Toronto, Ontario. University of Toronto.

investigators despite dedicating a large volume of resources.[126] Further, due to their highly controlled nature, traditional trials may not accurately reflect routine clinical practice or variability of practices across units. This highlights the need for alternative strategies to develop evidence in this patient population. Potential solutions that may be explored include establishing multicenter prospective data registries to collect highly granular data including TNE variables, innovative research methods such as comparative effectiveness research, and predictive machine learning.

CONCLUSIONS
Cardiovascular dysfunction is a common sequala sequela to sepsis. Among neonates, the diverse hemodynamic manifestations are a product of variable inflammatory pathways, cardiac immaturity, and hormonal responses. The classic assessment of warm vs. cold shock provides many clinical clues about the underlying cardiovascular derangements; although these are often thought of as two dichotomous entities, they are mediated by the same complex inflammatory cascade. As such, the clinical picture can evolve during the sepsis course, likely reflecting the relative dominant physiologic pathway at the time of clinical assessment. In the absence of high-quality evidence to support the initiation of therapeutic strategies, management of hemodynamic instability in neonatal sepsis should be done after careful consideration of the underlying

pathophysiology and individualized to the patient. The use of TNE may help corroborate clinical hemodynamic variables, add to our existing knowledge regarding mechanisms of action of common therapies used for hemodynamic instability, and support our understanding of short- and long-term outcomes in infants with abnormal cardiovascular health states.

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A.K. and A.J. both conceived and designed the review. A.K. drafted the manuscript and A.J. revised it critically. Both A.K. and A.J. approve the final version as submitted.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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