REVIEW ARTICLE

Hemodynamic Management Strategies in Pediatric Septic Shock: Ten Concepts for the Bedside Practitioner

Suchitra Ranjit, Rajeswari Natraj

Pediatric Intensive Care Unit, Apollo Children's Hospitals, Chennai, Tamil Nadu, India.

ABSTRACT

The three pathophysiologic contributors to septic shock include varying combinations of hypovolemia (relative > absolute), decreased vascular tone or vasoplegia, and myocardial dysfunction. The three pillars of hemodynamic support include fluid boluses, vasopressors with or without inotrope infusions. The three end-points of hemodynamic resuscitation include an adequate cardiac output, adequate mean arterial pressure (MAP) and diastolic blood pressure (DBP) for organ perfusion, and avoiding congestion (worse filling) parameters. Only 33-50% of septic patients show post-fluid bolus CO improvements; this may be sustained in ≥ 10% on account of sepsis-mediated glycocalyx injury. A pragmatic approach is to administer a small bolus (10 mL/kg over 20-30 min) and judge the response based on clinical perfusion markers, pressure elements, and congestive features. Vasoplegia marked by low DBP is a major contributor to hypotension in septic shock. Hence, a strategy of restricted fluid bolus with early low-dose norepinephrine (NE) (0.05-0.1 µg/kg/min) can be helpful. NE may also be useful in septic myocardial dysfunction (SMD) as an initial agent to maintain adequate coronary perfusion and DBP while minimizing tachycardia and providing inotropy. Severe SMD may benefit from additional inotropy (epinephrine/dobutamine). Except vasopressin, most vasoactive drugs may safely be administered via a peripheral route. The lowest MAP (5th centile for age) may be an acceptable target, provided end-organ perfusion is satisfactory. A clinical individualized approach combining the history, serial physical examination, laboratory analyses, available monitoring tools, and repeated assessment to individualize circulatory support may to lead to better outcomes than one-size-fits-all algorithms.

Keywords: *Hemodynamics, Fluids, Restrictive, Norepinephrine*

Published online: Jan 09, 2024; ***PII***: S097475591600586

Sepsis is a leading cause of morbidity, mortality, and hospitalization for children worldwide with > 80% of sepsis occurring in lower- and middle-income countries (LMICs) [1]. The 2020 Pediatric Surviving Sepsis Guidelines Campaign (peds-SSC) compiled evidence-based recommendations [2]. However, there was only limited evidence to guide the care in healthcare settings such as India with only few trained pediatric intensivists and level 1 and 2 pediatric intensive care units (PICUs) and fewer level 3 PICUs, even vastly insufficient for the vast Indian pediatric population, which occupy a vast middle ground between high-income countries and health facilities where the 'Fluid Expansion as Supportive Therapy (FEAST) study' was conducted [3]. In this article we will discuss ten concepts in the hemodynamic management of pediatric septic shock that may be helpful for the bedside pediatrician.

1. Pathophysiology of sepsis and septic shock

Sepsis and septic shock occur because of a dysregulated host response to not just bacterial infections but also viral, fungal, and parasitic infections. The ensuing inflammatory response is a complex interaction between the inciting pathogen, the host immune response, pro- and anti-inflammatory cytokines, among others. The severity and response to treatment may be altered by host and pathogen factors such as age, genetic susceptibility, microbial load, virulence etc. A dysregulated host response may be recognized by the presence of multi-organ dysfunction, often remote from the infective focus. Cardiovascular dysfunction in the setting of sepsis, called as septic shock, represents the severest form of sepsis. Clinical features of pediatric septic shock may have a combination of 3 or more of the following: tachycardia (which is persistent and disproportion to fever), decreased peripheral perfusion, with feeble/absent or bounding peripheral pulses, low or normal mean arterial pressure (MAP), altered consciousness /irritability, capillary refill time (CRT) that is flash or prolonged > 2 seconds, mottled or cool extremities, and decreased urine output [4].

Children, like adults, may have various clinical phenotypes, of which the vasoplegic/vasodilatory phenotype of septic shock may be most common [5]. The three

Correspondence to: Dr. Suchitra Ranjit,
Apollo Children's Hospital, Chennai, Tamil Nadu, India.
suchitraranjit@yahoo.co.in

fundamental pathophysiologic contributors to septic shock include hypovolemia, decreased vascular tone (or vasoplegia), and cardiac dysfunction [5,6]. However, these may not be clinically obvious at presentation, and may dynamically progress during the initial 24-48 h.

The three main pillars of cardiovascular support include fluid bolus (FB) administration to restore adequate circulating volume, vasopressor infusions to maintain vasomotor tone, and inotropes to improve cardiac contractility.

The three end points/goals of effective hemodynamic resuscitation include an adequate cardiac output (CO); the clinical markers of which include a good extremity perfusion, and normal CRT, a sufficient MAP and diastolic blood pressure (DBP) to ensure adequate organ perfusion, and avoiding worsening of filling (respiratory) parameters, as discussed further. Furthermore, shock resuscitation must optimize both macrocirculatory variables (CO, MAP) as well as microcirculatory parameters (regional blood flow distribution), of which capillary refill time (CRT) may be a surrogate [7].

2. Early recognition, screening tools and initial stabilization

Most childhood infections are not associated with cardiovascular failure (septic shock) or other organ failure. Only a small minority may progress to septic shock; early recognition of this subset based on certain "Red flags" is imperative so that immediate resuscitation is instituted. Pediatricians must have age-appropriate vital parameter values (**Table I**) prominently displayed in their clinics and wards so that the frontline caregivers are able to identify those in need of urgent intervention. Implementation of a septic shock identification/screening/trigger tool [8] which combines various conditions (e.g., high-risk patient conditions, abnormal vital signs, and/or physical findings) may help prompt further evaluation or referral.

3. Circulating volume in septic shock and the response to fluid boluses

There are differences in hypovolemia in fluid-losing states compared to septic shock. Fluid losses in the former (e.g., diarrhea/vomiting) results in absolute hypovolemia. Here the fluid losses lead to decreased venous return (VR) and thereby decreased CO, with compensatory rise in systemic vascular resistance (SVR), recognized clinically by cold extremities with narrow pulse pressures [4]. Fluid replacement leads to improved VR, CO and normalization of the elevated SVR.

However, septic shock is not a primary fluid-losing state, and relative hypovolemia (due to redistributed blood volume) is far more common than absolute hypovolemia [8,9]. Moreover, the SVR is often low in septic shock, this is discussed further below. The response to fluid bolus (FB) is variable in septic shock. Disruptions of the inner lining of the vascular endothelium are unique to inflammatory states including sepsis [10]. Glycocalyx injury increases vascular permeability, and interstitial fluid shifts may be further potentiated when FB are rapidly administered [10]. Interestingly, while FB generally corrects hypotension in both hypovolemic states as well as septic shock, in some patients, fluid loading itself may potentiate sepsis-associated vasoplegia, and lead to lower MAP and diastolic BP [11,12]. Adverse effects of large-volume fluids may be observed in several organs, including the cardiovascular system, lungs, and brain [13]. Moreover, fluid-induced hemodilution may result in paradoxical decrease in tissue oxygen delivery [14].

The variable response to FB in septic shock suggests that, after the initial 20mL/kg bolus (provided in two aliquots of 10 mL/kg each), every subsequent bolus must be earned, rather than being automatically prescribed.

Fluid bolus prescriptions in septic shock

Cautious initial fluid resuscitation using isotonic crystalloids at 10 mL/kg over 20-30 min may be safely administered, and the response carefully monitored. If there is no worsening, and the history indicates ongoing fluid losses (diarrhoea ± vomiting), the FB may be repeated and titrated to match the losses [15].

Fluid type

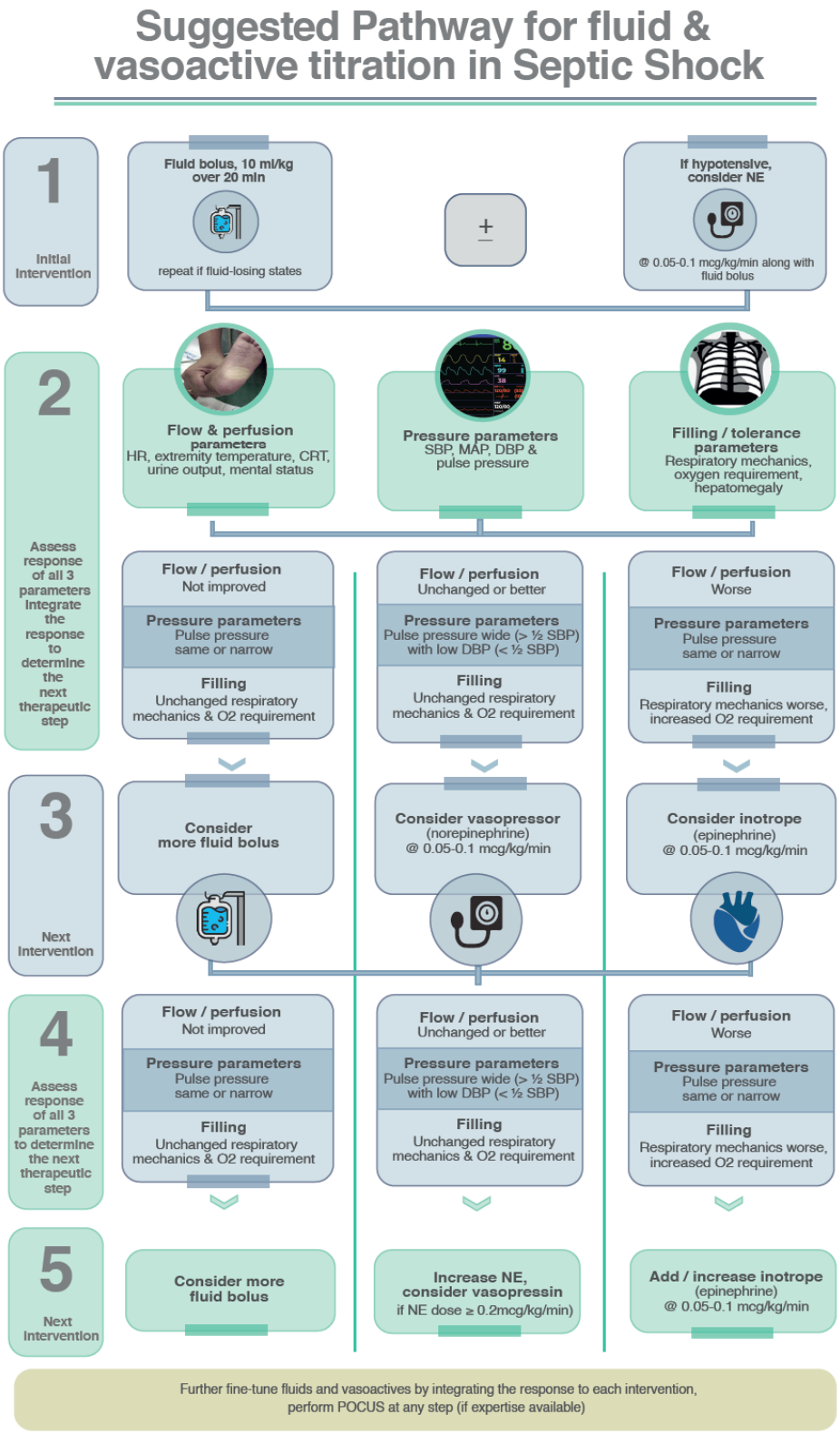
Large volumes of normal saline may induce hyperchloremic acidosis and increased incidence of acute kidney injury [16]. However, if lower volumes (< 20 mL/kg) are infused, these complications are unlikely, and therefore the choice of crystalloid may not matter [17].

Monitoring the response to FB

During FB administration, trends in clinical perfusion

Table I Age-appropriate vital parameter values

Vital sign parameter	*Age < 1 y*	*1-5 y*	*≥5-10 y*	*≥10-16 y*	*≥16 -18 y*
Heart rate (beats/min) *(Upper limit of normal)*	180	140	120	100	90
Minimum systolic blood pressures (<5th centile (mmHg)	<70	(70 + age) × 2	(70 + age) × 2	90	90
Respiratory rate (breath/min) *(Upper limit of normal)*	60	40	30	30	16



BP: Blood pressure; CO: Cardiac output; CRT: Capillary refill time; DBP: Diastolic blood pressure; HR: Heart rate; MAP: Mean arterial pressure; NE: Norepinephrine; POCUS: Point of care ultrasound; SBP: Systolic blood pressure

Fig. 1 Suggested pathway for fluid and vasoactive agent titration in pediatric septic shock

Table II Ten Commandments for Fluid Bolus (FB) Administration in Septic Shock

	Clinical concepts	*Clinical considerations*	*Implications at the bedside*
1	Hypovolemia in fluid-losing states (e.g., vomiting, diarrhea, hemorrhage) results in absolute hypovolemia	•Absolute hypovolemia: fluid is lost from the body. •Absolute hypovolemia may also occur in capillary leak states: fluid is lost from the vascular compartment. • Large-volume fluid loss may result in hypotension.	• In fluid-losing states, rehydration restores circulating volume, preload, and CO. • Rehydration should aim to match ongoing losses. • Larger volume FB is indicated if the patient is hypotensive.
2	Hypovolemia in septic shock	• Relative >> absolute hypovolemia. • Fluid is re-distributed in dilated venous capacitance vessels (distributive shock). • Hypotension in septic shock reflects low vascular tone rather than large volume fluid deficits.	• In septic shock, an initial fluid bolus of 10 mL/kg +10 mL/kg is reasonable as it addresses the minor element of absolute hypovolemia. • Hypotension in septic shock is best addressed by low dose norepinephrine (rather than large volume FB).
3	The goal of FB in shock is to increase the CO, and thereby improve tissue O2 delivery.	• In septic shock, FB increases the CO in only ~ 50% (i.e., fluids have no benefit in the remaining half, and may harm). • Even if the CO increases, the response may be sustained in < 10% by 60 min.	• Disruptions in glucocalyx (which has a gate-keeper role) may explain the failure of CO rise after FB is septic shock. • Each infused FB may further damage the glycocalyx, leading to further increase capillary leak.
4	Vascular tone changes after FB	• The BP response to FB may be unpredictable. • FB may improve BP parameters in most. • FB may have a vasodilatory effect in some septic patients. • MAP (or DBP) defines the perfusion pressure gradient in many vital regions.	• The clinician must monitor changes in pressure parameters after FB in addition to perfusion markers. • If the MAP ± DBP falls after FB, further FB must be discontinued. • Alternative strategies such as vasoactive infusion may be considered.
5	Monitoring the CO response to fluid bolus	Fluid-responsiveness (FR) tests aim to predict which patients will respond with increase in CO after FB.	• If the FR tests negative, unnecessary FB can be avoided in non-responders.
6	*Static tests* for FR	• CVP is the best-known static test for FR. • CVP principally reflects myocardial function, and is around zero in patients with normal heart function.	• CVP has fallen out of favour as it is unreliable as an intra-vascular volume indicator. • A significant increase in CVP after FB a should raise suspicion of myocardial dysfunction.
7	*Dynamic tests* for FR	• Dynamic FR tests rely on heart-lung interactions and are based on the principle of inducing brief changes in cardiac pre-load, and then observing for increase in CO. •In a fluid responsive patient, CO increases by 10-15% from baseline.	• Dynamic FR tests use the respiratory variation of the arterial line waveform (pulse pressure variation or PPV).
8	Dynamic tests: limitations	• Dynamic tests require many pre-conditions that may be impractical (Invasive ventilation, no spontaneous breathing etc)	• Dynamic FR tests are not practical to perform in clinical practice. • CO changes are challenging to measure. • Right ventricular (RV) dysfunction may cause false a FR positive test. Here, fluid loading can be harmful.
9	Fluid overload vs fluid intolerance	• Fluid overload (FO) describes a patient who develops respiratory deterioration when too much fluid administered (hypervolemia). • However, in severe capillary leak states	• Strategies for fluid intolerance depends on the cause. • In the setting of capillary leak, consider continued slow filling, colloids and (non-invasive) respiratory support.

contd...

from pre-page

	Clinical concepts	*Clinical considerations*	*Implications at the bedside*
		(dengue shock), respiratory status deterioration may occur even when the patient is still hypovolemic. A preferred term is fluid-intolerance (FI).	
10	A restrictive fluid administration protocol + early vasoactive infusion may be beneficial for the patient	• If septic shock unresolved after FB upto 20mL/kg or if hypotension is present, early vasoactive support is recommended rather than giving more FB. • In hypotensive septic shock, concurrent vasoactive (with FB) achieves rapid control of the BP and perfusion.	Restrictive fluids + early vasoactive regimen may decrease the need for PICU organ support (ventilation, dialysis).

BP: Blood pressure; CO: Cardiac output; CRT: Capillary refill time; CVP: Central venous pressure; DBP: Diastolic blood pressure; HR: Heart rate; ICU: Pediatric intensive care unit; MAP: Mean arterial pressure; SBP: Systolic blood pressure

markers, pressure elements, and filling (evidence or fluid overload/ fluid intolerance) must be monitored (**Fig. 1**).

Table II illustrates the considerations for fluid bolus in septic shock.

4. Decreased vascular tone or vasoplegia

A cardinal mechanism of vasodilatory/vasoplegic shock is vascular smooth muscle relaxation. The vasoplegic syndrome is encountered in many clinical scenarios, including post-cardiac bypass, after burns and trauma [18], and may be present to variable degrees in pediatric septic shock, with an Indian study reporting vasodilatory shock in more than 85% children [5]. Vasoplegia or pathologically low systemic vascular resistance (SVR) is the major contributor of hypotension in septic shock, and is recognized by low DBP with low or normal MAP, wide pulse pressures (PP) [PP > Systolic Blood Pressure (SBP) / 2] and bounding extremity pulses [5,19].

Vasoplegia must be rapidly corrected to prevent organ hypoperfusion. Organ perfusion is determined by the pressure gradient perfusing each organ, for example, cerebral perfusion pressure is determined by the difference between the MAP and intracranial pressure (ICP), and the renal perfusion pressure is the difference between MAP and central venous pressure (CVP). A low DBP is a readily available marker of low arterial tone in septic shock, however, clinicians often focus on the SBP and MAP, and overlook the DBP [20]. A low DBP may decrease coronary perfusion with co-existing tachycardia doubling the detrimental effects on the heart [21]. DBP < 50 mmHg is considered low in adults and age-appropriate pediatric DBP cut-offs have been reported in the 2020 Pediatric Advanced Life Support (PALS) Manual [4]. DBP ≥ 25 mmHg in infants and ≥ 30 mmHg children aged ≥ 1 y was associated with survival after cardiopulmonary resuscitation (CPR) [22].

The pulse pressure (PP = SBP - DBP) correlates with stroke volume (SV), and clinicians may suspect a high SV typical of a vasodilatory circulation if the pulse pressure is high. Conversely, if the PP is narrow, a low SV from either hypovolemia ± decreased cardiac function may be present.

Clinicians must be mindful that well-intended therapies that aim to correct hypotension/hypoperfusion can exacerbate vasodilatation and lead to lower BP in some patients. For example, fluid resuscitation itself may have a vasodilatory effect [23,24] possibly due to glycocalyx injury [25]. Inodilators such as milrinone may improve the CO/forward flow but can vasodilate and decrease organ perfusion pressures [26].

A low SVR is the major contributor of hypotension in septic shock [27]. While large-volume FB is often recommended in the presence of hypotension or cardiovascular collapse [2], a preferred pathophysiological strategy may be the prompt start of vasopressor such as norepinephrine concurrently with, or soon after the initial FB [10,27].

The administration of stress-dose steroids is controversial [2], but may improve vasoactive responsiveness, and is often administered if shock is unresolved despite initial fluid and vasoactive support. Intravenous hydrocortisone (1 mg/kg/dose q6h; max 50 mg) may be commenced when the second pressor is being started. Earlier steroid administration (within the 1st h) is helpful in chronic steroid-dependent patients.

Table III summarizes the pathophysiology and consequences of vasoplegia in septic shock.

Table III Pathophysiology and Consequences of Vasoplegia in Septic Shock

Pathophysiology	*Consequences*	*Implications for the clinician*
Vasodilatation is major player in septic shock	Low arterial tone leads to hypotension (low MAP[a], low DBP[b]).DBP is a useful marker of arterial tone, but rarely given importance	Low arterial tone may be recognized at presentation, or after fluid loading. Physicians must monitor MAP as well as DBP
Vasodilatation can affect arterial and venous capacitance vessels	Vasoplegia of venous capacitance vessels is the main cause of "relative" hypovolemia and distributive shock. Circulating volume accumulates in the expanded "unstressed" compartment, and venous return decreases	Large volume FB can improve venous return, but effects are ill-sustained. Low dose pressors (NE) addresses the deranged pathophysiology and can improve venous return and CO in a sustained manner. Early vasoactives can have a "fluid-sparing" effect, and decrease the need for ICU resources
Unintended consequences of common therapies: Vasoplegia may worsen with FB or inodilator agents	FB may potentiate vasoplegia and convert a hypodynamic to hyperdynamic circulation. Inodilators such as milrinone can also potentiate vasoplegia.	If the MAP and/or DBP falls after FB, initiate early vasoactive (NE) rather than repeated FB. For myocardial dysfunction, epinephrine may be preferable to inodilators. Avoid inodilator agents, if possible, during the initial 24 h. Even if dobutamine used, combination with pressor may help safeguard against hypotension.
Organ perfusion suffers most when upstream pressure is low (low MAP/ DBP) and downstream pressures are high (high CVP or venous congestion)	Venous congestion due to RV dysfunction may be seen in 25% of ventilated patients with pneumonia/ARDS	Therapeutic strategies to optimise organ perfusion pressure include maintaining adequate MAP/DBP with consideration for early decongestion to lower venous pressures. Hypotension with low MAP and/or DBP must be corrected rapidly.

ARDS: Acute respiratory distress syndrome; BP: Blood pressure; CO: Cardiac output; CVP: Central venous pressure; DBP: Diastolic blood pressure; FB: Fluid bolus; MAP: Mean arterial pressure; NE: Norepinephrine; RV: Right ventricular; SBP: Systolic blood pressure; SVR: Systemic vascular resistance

[a]*Minimum MAP (mmHg) for age:* 1-6 mo: > 40; 7-12 mo: > 45;
MAP (5th percentile at 50th height percentile) = 1.5 × age in years + 40.
For CNS infections with raised ICP: MAP (50th percentile at 50th height percentile) = 1.5 × age in years + 55 [11,50]
[b]*Minimum DBP for age* [3]

5. Cardiac derangements in septic shock and the importance of 'loading' conditions

Septic myocardial dysfunction (SMD) may be present in 40-50% of septic shock patients [28]. Left ventricular (LV) systolic dysfunction is most commonly described, however LV diastolic dysfunction and right ventricular (RV) systolic dysfunction may also be present, both of which have higher mortality [29,30].

Myocardial dysfunction in septic shock has several important differences from typical cardiogenic shock due to viral myocarditis. Viral myocarditis presents with low CO, compensatory high SVR (manifesting as narrow pulse pressures and poor extremity perfusion), elevated filling pressures (recognized by early pulmonary edema), and low mixed venous saturations reflecting high tissue oxygen extraction. The cardiovascular support in viral myocarditis emphasizes inodilator use and diuretics.

In contrast, the manifestations of SMD (typically LV systolic dysfunction) are crucially dependent on loading conditions: preload (volume status) and more importantly the afterload or SVR [31]. This explains why at presentation, when the afterload is low, the poor LV function may not be clinically obvious. The low afterload promotes forward flow and 'masks' clinical features of SMD, which may become 'unmasked' when the low afterload is raised with pressors. Other features of SMD include normal or even elevated mixed venous saturations (due to decreased tissue oxygen extraction) [5,32] and reduced ventriculo-arterial coupling [33].

While the low SVR promotes forward flow in patients with SMD, there is a potential for coronary ischemia if the DBP is too low. In this setting, the overarching therapeutic goals are to maintain an adequate coronary perfusion/DBP, minimize myocardial demands (tachycardia control) while providing some inotropy. Low-dose norepinephrine (NE) (0.05- 0.1 µg/kg/min) infusion may fulfil these goals in patients with mild/moderate SMD, as it has alpha-mediated vasoconstriction, minimal chronotropy, modest inotropy, and improves ventriculo-arterial coupling

without imposing excess afterload [21,34]. However, in patients with severe SMD, the cardiac function may deteriorate after NE initiation, and inotropy may be indicated.

The impact of norepinephrine on cardiac function depends on the balance between the potentially beneficial effects (improved ventriculo-arterial coupling, increased coronary artery perfusion, modest inotropy) vs the higher afterload [33,35]. A safe strategy is to start with the lowest dose of norepinephrine (0.05 µg/kg/min) and carefully monitor the patient's flow/pressure and filling parameters in conjunction with serial echocardiography (**Fig. 1**) to identify patients who require additional inotropy.

Low-dose epinephrine 0.05 - 0.1 µg/kg/min, or dobutamine 5-10 µg/kg/min may be useful, while continuing norepinephrine 0.05 - 0.2 µg/kg/min for coronary perfusion; the combination may successfully restore the hemodynamics in this challenging subset with combined SMD and vasoplegia.

Inodilator use (milrinone) can be especially deleterious in the initial 24 h given its vasodilatory effect and longer-half-life (compared to catecholamines), and may be best considered after the initial 1-2 days.

6. Choice of initial vasoactive in pediatric septic shock

Catecholamine vasoactive agents are the most popular agents in the ER and ICU as they have a rapid onset, and more importantly, a very short offset/half-life (2-3 minutes). While life-saving, they are extremely potent, with a narrow therapeutic index and several potentially lethal complications [36]. An individualized approach considering the risk-benefit profile, using minimal effective doses to achieve precise therapeutic targets, and attempts to discontinue these agents as soon as possible is important**.**

Most vasoactives (except vasopressin) may safely be administered via a peripheral route provided a well-secured, clearly-labelled, largest bore intravenous (IV) catheter proximal to the elbow is used, and this line is dedicated only to diluted-strength vasoactive infusions [37]. Intraosseous infusions may be used until intravenous access is secured. If vasoactive infusions are required for > 6-12 h duration, a central line may be necessary, unless the circulatory parameters are clearly improving. Training of healthcare staff in the handling of vasoactives infusions whether infused via a peripheral or central line is mandatory to minimize complications.

Epinephrine or norepinephrine?

Epinephrine was previously considered a preferred agent in pediatric septic shock, as its powerful inotropy may address SMD, and also co-existing vasoplegia at higher doses (≥0.2µg/kg/min). However, epinephrine-induced sympathetic overstimulation often increases tachycardia, worsens markers of myocardial injury and myocardial oxygen demand [38], and has been reported to be associated with higher mortality in adults [39].

Norepinephrine with its potent α_1-adrenergic pressor effects with mild β-agonist mediated inotropy is highly beneficial in the initial phase of resuscitation [33], and is used as a first-line agent in pediatric septic shock by many pediatric intensivists [40]. Norepinephrine can improve vascular tone (and thereby the DBP/MAP), increase venous return by reversing the distributive shock, support coronary perfusion and myocardial contractility, improve ventriculo-arterial coupling and help sustain CO and tissue perfusion [41]. Norepinephrine doses between 0.05-0.2 µg/kg/min are generally safe; higher doses can increase the blood pressure, but may worsen the cardiac function and decrease the micro-circulatory perfusion by excess vasoconstriction [35].

Myocardial depression may become clinically evident in some patients when the hypotension is corrected, and if more inotropy is considered necessary, epinephrine or dobutamine may be added depending on the BP parameters (**Fig. 1**).

If hypotension with persistent low DBP suggestive of persistent vasoplegia is observed even on norepinephrine, vasopressin infusion at 0.0005-0.002 units/kg/min may be added; stress dose steroids initiation may improve the efficacy of pressor agents [27].

7. Endpoints of therapy and hemodynamic monitoring

The same signs of poor perfusion that are used to recognize shock are also useful to determine the patient's response, and a combination of perfusion and pressure parameters may indicate shock reversal.

In some patients, tachycardia may persist long after other parameters have normalized. Similarly, hyperlactatemia may have causes other than tissue hypoperfusion. Moreover, lactate clearance may be delayed in sepsis [42]. Therefore, isolated tachycardia or hyperlactatemia without other signs of hypoperfusion should not be aggressively treated, but carefully observed. CRT normalization may be better than lactate as an end-point for septic shock resuscitation [7].

A Foley's catheter must be inserted early, and hourly urine trends charted. Normal urine flow is reassuring as an indicator of adequate perfusion, unless hyperglycemia,

kidney injury, or recent diuretic administration is present.

Invasive arterial monitoring is more accurate than non-invasive blood pressure (NIBP) monitoring, but may have logistic issues. The reliability of NIBP is often questioned, but may be increased by using age-appropriate arm cuffs (rather than lower limb), and taking more than one measurement [43,44]. With respect to target MAP, the lowest MAP (5th centile for age) may be accepted provided end-organ perfusion (mental status, extremity perfusion, urine output, etc) are satisfactory. While this strategy may be helpful to avoid high-dose vasoactives, a higher MAP (≥50th centile for age) may be necessary in the presence of raised intracranial pressure, right ventricular failure or venous congestion.

Once the end-points of shock resuscitation have been reached, it is important to expeditiously begin vasoactive weaning and discontinuation. However, given the lack of evidence, there is a variability in the practice regarding weaning and discontinuation of vasoactive support. After circulatory parameters have resolved, a rapid vasoactive taper and discontinuation over 3-6 h with careful monitoring for shock recurrence is practiced in some centres, while other centres maintain vasoactive support for 24-48 h prior to start of wearing. Any recurrence of instability during weaning should prompt re-start of vasoactive support and workup of unresolved shock described in #10 below. If vasopressin has been used, it should be weaned last [27].

8. Bedside approach to fluid and vasoactive titration

A clinical individualized approach combining the history, serial physical examination, laboratory analyses, available monitoring tools, and repeated assessment to individualize circulatory support may to lead to better outcomes than one-size-fits-all algorithms. The response to each therapeutic intervention (fluid/pressor/inotrope) may provide crucial information to decode the individual patient's underlying pathophysiology (**Fig.1**), even if echocardiography is unavailable. The clinician at the bedside must integrate information from changes in *"flow"* parameters (perfusion markers including CRT, limb/extremity temperature), *"pressure"* parameters (MAP, SBP, DBP, pulse pressure) and *"filling"* parameters (respiratory mechanics, oxygen requirement, hepatomegaly) in response to each intervention [6].

a) For example, the initial FB may be considered a *"fluid test"*, and evaluation of flow/pressure/filling parameters may help to determine the next best therapeutic step.

- If the administered FB is insufficient to match fluid losses, hypoperfusion will persist with narrow pulse pressures and unchanged lung mechanics. Those with significant myocardial dysfunction may exhibit continued poor perfusion with narrow pulse pressure but with worsened respiratory mechanics. In patients with a hyperdynamic phenotype, the FB may either lead to unchanged pressure parameters or lead to lower DBP by worsening/unmasking the vasoplegic state.
- However, if the underlying pathophysiology is unclear after the initial 10-20 mL/kg fluid, it is reasonable to start with a low dose norepinephrine infusion (0.05-0.1 µg/kg/min), given that 85% of children with septic shock are vasodilated despite a clinical "cold shock" phenotype, and about 50% have decreased myocardial function [5].

b) Norepinephrine may be initiated at 0.05-0.1 µg/kg/min as an initial vasoactive, here the norepinephrine may be considered as a *"pressor test"* and analysis of flow/pressure/filling parameters helps to determine the next therapeutic step.

- Many children, including those with mild myocardial dysfunction, improve after the combination of modest initial fluid bolus + norepinephrine infusion [34]. However, a few patients may require one or more of three additional therapies: more fluid, more pressor and/or more inotropy.
- More fluid at 10mL/kg aliquots may be provided, especially if there is history of ongoing fluid-loss.
- Additional pressor support may be required if the integrated flow/pressure/filling parameters indicate continuing vasoplegic shock (flow parameters indicating bounding pulses, pressure parameters indicate low DBP with wide pulse pressures, and filling parameters unchanged). Options include increasing norepinephrine dose to 0.2 µg/kg/min and/or adding vasopressin.
- More inotropy may be helpful in a child with low volume pulses, prolonged CRT, low/normal MAP and DBP with narrow pulses pressures, and filling parameters indicating lung congestion (worsened respiratory mechanics, increased oxygen requirement). Inotrope choice includes either epinephrine or dobutamine depending on the pressure parameters.

c) Epinephrine at doses of 0.05-0.2 µg/kg/min may be started as the first-line vasoactive after initial fluid bolus as an *"inotrope test"*, and if shock is unresolved, analysis of flow/pressure/filling parameters helps to

determine the next therapeutic step. Improved perfusion as well as pressure parameters indicate that epinephrine is helping. In non-responders, worsening tachycardia ± fall in pressure parameters may warrant re-evaluation. Hypotension may occur as epinephrine's alpha-effect may be insufficient to address vasoplegia unless higher doses (> 0.2 µg/kg/min) are used. In this subset, as well in patients with complex pathophysiology, Point-of-Care Ultrasound (POCUS) performed by experienced personnel may be helpful.

9. Respiratory support

Similar to other life-threatening conditions in children, the physician must assess if the airway patency is satisfactory, if oxygen supplementation is required, and assess the patient's respiratory drive and work of breathing. Patients with refractory shock with/without worsening respiratory status may require additional respiratory support, and a trial of non-invasive positive pressure ventilation (NIPPV) or high-frequency nasal cannula oxygen (HFNC) support can improve oxygenation and decrease the work of breathing in some patients.

However, close patient monitoring and education of all healthcare staff is essential, as children whose cardiorespiratory status fails to improve within the initial 1-2 h of initiating NIPPV/HFNC are a high-risk subset with high mortality risk unless expert intubation and controlled ventilation is expeditiously carried out [45]. Early referral to a higher facility must be considered if the cardiorespiratory status is not improving.

Indications for intubation and positive pressure ventilation (PPV) are variable, and usually include cardiopulmonary arrest, deteriorating mental status with a Glasgow Coma Score ≤8, inability to maintain a patent airway, and refractory shock with escalating lactate levels despite optimizing fluids and vasoactive support.

It should be understood that PPV may not always be beneficial in septic shock. The transition from spontaneous breathing to controlled PPV after intubation can worsen shock by decreasing venous return. Further, the adverse effects of sedative drugs can lead to worsening vasodilation and myocardial depression. Preserving the patient's spontaneous respiratory drive may preferable in some, unless the criteria listed above are met.

The act of intubation of the hypoxemic, shocked, acidotic patient can be fraught with complications including worsening hypoxemia, hypotension, aspiration, and cardiac arrest [46]. A high risk intubation protocol including peri intubation positive pressure/HFNC, preemptive vasoactive infusions/push-pressors, and low-dose ketamine may mitigate the peri-intubation risks [46]. After intubation, attempts to minimize secondary infections, and promote ventilator liberation at the earliest opportunity remain important.

10. Unresolved shock

Many inter-related conditions may be at play when shock is unresolved, including pre-existing morbidities, type of invading pathogen and delayed hospitalization. A comprehensive discussion is not possible, but physicians need to carefully review for correctable causes, including alternative diagnosis, inadequate source control, unrecognized additional foci of infection, inappropriate antimicrobial therapy, relief of pleural/pericardial tamponade or compartment syndromes, and need for blood transfusion and/or steroids [47].

The use of high vasoactive doses is common in refractory shock. However, catecholamine toxicity may paradoxically contribute to the circulatory instability. If the hypotension worsens as catecholamine vasoactives doses are being increased (with/without pulmonary edema), the clinician should consider whether underlying diastolic dysfunction or dynamic left ventricular output obstruction is present [48]. Improved survival has been described by the use of non-catecholamine agents (vasopressin, milrinone), slow filling, and gradual catecholamine down-titration guided by Doppler echocardiography [49]. While extra-corporeal support may be available in some centres for refractory shock, family discussions must emphasize realistic expectations (prognosis and costs).

CONCLUSION

In order to reduce high sepsis mortality, efforts to improve early recognition and administration of the early bundle remain the key pillars of initial support. If signs of shock persist, a more individualized approach to hemodynamic resuscitation focusing on early use of vasoactives and limiting further fluid bolus therapy may be of benefit. There remains an urgent need for trials in low- and middle-income countries (LMICs) to explore the merits of an individualized approach.

Acknowledgements: The authors express their appreciation to our outstanding PICU consultant colleagues at Apollo Children's Hospital, including Dr Priyavarthini V, Dr Vasanth Kumar and Dr L Chidhambharam. We are also grateful to Dr Anita T, Consultant, Pediatric Emergency Department, all our enthusiastic PICU fellows and physician assistant and nurses. We thank Mr Hariprasad G for his expertise in creation of the **Fig. 1.**

Funding: None; *Competing interests*: None stated

REFERENCES

1. Fleischmann-Struzek C, Goldfarb DM, et al. The global

burden of paediatric and neonatal sepsis: a systematic review. Lancet Respir Med./ 2018;6:223-30.
2. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Pediatr Crit Care Med. 2020;21:e52-106.
3. Maitland K, Kiguli S, Opoka R, et al. Mortality after fluid bolus in African children with severe infection. N Engl J Med. 2011;364:2483-95.
4. Duff JP, Topjian AA, Berg MD, et al. 2019 American heart association focused update on pediatric advanced life support: an update to the American heart association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2019;140: E904-14.
5. Ranjit S, Aram G, Kissoon N, et al. Multimodal monitoring for hemodynamic categorization and management of pediatric septic shock: A pilot observational study. Pediatr Critic Care Med. 2014;15:1-10.
6. Ranjit S, Kissoon N, Argent A, et al. Haemodynamic support for paediatric septic shock: a global perspective. Lancet Child Adolesc Health. 2023;7:588–98.
7. Zampieri FG, Damiani LP, Bakker J, et al. Effects of a resuscitation strategy targeting peripheral perfusion status versus serum lactate levels among patients with septic shock a bayesian reanalysis of the ANDROMEDA-SHOCK trial. Am J Respir Crit Care Med. 2020;201:423–9.
8. Perner A, Cecconi M, Cronhjort M, et al. Expert statement for the management of hypovolemia in sepsis. Intensive Care Med. 2018;44:791-8.
9. Hilton A, Bellomo R. A critique of fluid bolus resuscitation in severe sepsis. Crit Care. 2012;16:302.
10. Hippensteel JA, Uchimido R, Tyler PD, al. Intravenous fluid resuscitation is associated with septic endothelial glycocalyx degradation. Crit Care. 2019;23:259.
11. Ranjit S, Natraj R, Kissoon N, et al. Variability in the hemodynamic response to fluid bolus in pediatric septic shock. Pediatr Crit Care Med. 2021;22:e448-58.
12. Monge García MI, Guijo González P, Gracia Romero M, et al. Effects of fluid administration on arterial load in septic shock patients. Intensive Care Med. 2015;41:1247-55.
13. Levin M, Cunnington AJ, Wilson C, N et al. Effects of saline or albumin fluid bolus in resuscitation: evidence from re-analysis of the FEAST trial. Lancet Respir Med. 2019;7: 581-93.
14. Reuter D, Chappell D, Perel A. The dark sides of fluid administration in the critically ill patient. Intensive Care Med. 2017;44:1-3.
15. World Health Organization. Guideline: Updates on Paediatric Emergency Triage, Assessment and Treatment: Care of Critically-Ill Children. Geneva: World Health Organization; 2016. Accessed on Aug 03, 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK350528/
16. Sankar J, Muralidharan J, AV L, et al. Balanced crystalloids versus saline for initial fluid resuscitation in children with septic shock. Crit Care Med. 2020;49:17.
17. Monnet X, Lai C, Teboul JL. How I personalize fluid therapy in septic shock? Crit Care. 2023;27:123.
18. Lambden S, Creagh-Brown BC, Hunt J, et al. Definitions and pathophysiology of vasoplegic shock. Crit Care. 2018; 22:174.
19. Hernandez G, Messina A, Kattan E. Invasive arterial pressure monitoring: much more than mean arterial pressure! Intensive Care Med. 2022;48:1495-7.
20. Hamzaoui O, Shi R. Early norepinephrine use in septic shock. J Thorac Dis. 2020;2:S72-7.
21. Ospina-Tascón GA, Teboul JL, Hernandez G. et al. Diastolic shock index and clinical outcomes in patients with septic shock. Ann Intensive Care 2020;10:41.
22. Berg RA, Sutton RM, Reeder RW, et al. Association between diastolic blood pressure during pediatric in-hospital cardiopulmonary resuscitation and survival. Circulation. 2018;137:1784-95.
23. Cholley BP, Lang RM, Berger DS, et al. Alterations in systemic arterial mechanical properties during septic shock: role of fluid resuscitation. Am J Physiol. 1995;269:H375-84.
24. Ricard-Hibon A, Losser MR, Kong R, et al. Systemic pressure-flow reactivity to norepinephrine in rabbits: impact of endotoxin and fluid loading. Intensive Care Med. 1998;24:959-66.
25. Byrne L, Obonyo NG, Diab SD, et al. Unintended consequences: fluid resuscitation worsens shock in an ovine model of endotoxemia. Am J Respir Crit Care Med. 2018;198:1043-54.
26. Hollenberg SM. Vasoactive drugs in circulatory shock. Am J Respir Crit Care Med. 2011;183:847-55.
27. Hamzaoui O, Goury A, Teboul JL. The eight unanswered and answered questions about the use of vasopressors in septic shock. J Clin Med. 2023;12:4589.
28. Sanfilippo F, La Rosa V, Grasso C et al. Echocardiographic parameters and mortality in pediatric sepsis. Pediatr Crit Care Med. 2020;22:251-61.
29. Ventetuolo CE, Klinger JR. Management of acute right ventricular failure in the intensive care unit. Ann Am Thorac Soc. 2014;11:811-22.
30. Sankar J, Das R, Jain A, et al. Prevalence and outcome of diastolic dysfunction in children with fluid refractory septic shock—a prospective observational study. Pediatr Critic Care Med. 2014;15:e370-8.
31. Boissier F, Razazi K, Seemann A, et al. Left ventricular systolic dysfunction during septic shock: the role of loading conditions. Intensive Care Med. 2017;43:633–42.
32. Bouferrache K, Amiel JB, Chimot L, et al. Initial resuscitation guided by the Surviving Sepsis Campaign recommendations and early echocardiographic assessment of hemodynamics in intensive care unit septic patients. Crit Care Med. 2012;40:2821-7.
33. Foulon P, De Backer D. The hemodynamic effects of norepinephrine: far more than an increase in blood pressure! Ann Transl Med. 2018;6:S25.
34. Ranjit S, Natraj R, Kandath SK, et al. Early norepinephrine decreases fluid and ventilatory requirements in pediatric vasodilatory septic shock. Indian J Crit Care Med. 2016;20: 561-9.
35. De Backer D, Foulon P. Minimizing catecholamines and optimizing perfusion. Crit Care. 2019;23(Suppl 1):149.
36. Annane D, Ouanes-Besbes L, de Backer D, et al. A global

perspective on vasoactive agents in shock. Intensive Care Med. 2018;44:833-46.
37. Owen VS, Rosgen BK, Cherak SJ, et al. Adverse events associated with administration of vasopressor medications through a peripheral intravenous catheter: a systematic review and meta-analysis. Crit Care. 2021;25:146.
38. Vorovich E. Why is epinephrine not the drug of choice in cardiogenic shock? J Shock Hemodyn. 2022;1:E20221210.
39. Tarvasmäki T, Lassus J, Varpula M, et al. Current real-life use of vasopressors and inotropes in cardiogenic shock - adrenaline use is associated with excess organ injury and mortality. Crit Care. 2016;20:208.
40. Morin L, Kneyber M, Jansen NJG, et al. Translational gap in pediatric septic shock management: an ESPNIC perspective. Ann Intensive Care. 2019;9:73.
41. De Backer D PM. Norepinephrine improves cardiac function during septic shock, but why? Br J Anaesth. 2018;120:e421-4.
42. Marik PE BR. Lactate clearance as a target of therapy in sepsis: A flawed paradigm. OA Critical Care. 2013;1:3.
43. Lehman LW, Saeed M, Talmor D, Mark R, Malhotra A. Methods of blood pressure measurement in the ICU. Crit Care Med. 2013;41:34-40.
44. Duncombe S, Voss C, Harris K. Oscillometric and auscultatory blood pressure measurement methods in children: a systematic review and meta-analysis. J Hypertens. 2016; 35:1.
45. Inglis R, Ayebale E, Schultz MJ. Optimizing respiratory management in resource-limited settings. Curr Opin Crit Care. 2019;25:45–53.
46. Heffner AC, Swords D, Kline JA, Jones AE. The frequency and significance of postintubation hypotension during emergency airway management. J Crit Care. 2012;27:417.
47. Duke T. New WHO guidelines on emergency triage assessment and treatment. Lancet. 2016;387:721-4.
48. Slama M, Tribouilloy C, Maizel J. Left ventricular outflow tract obstruction in ICU patients. Curr Opin Crit Care. 2016;22:260-6.
49. Natraj R, Ranjit S. BESTFIT-T3: A tiered monitoring approach to persistent/recurrent paediatric septic shock – a pilot conceptual report. Indian J Crit Care Med. 2022; 26:863-70.
50. Haque IU, Zaritsky AL. Analysis of the evidence for the lower limit of systolic and mean arterial pressure in children. Pediatric Critical Care Medicine. 2007;8:138-44.