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# Hemodynamic monitoring and management of pediatric septic shock

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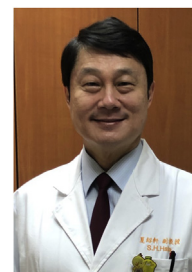
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ABSTRACT

Sepsis remains a major cause of morbidity and mortality among children worldwide. Furthermore, refractory septic shock and multiple organ dysfunction syndrome are the most critical groups which account for a high mortality rate in pediatric sepsis, and their clinical course often deteriorates rapidly. Resuscitation based on hemodynamics can provide objective values for identifying the severity of sepsis and monitoring the treatment response. Hemodynamics in sepsis can be divided into two groups: basic and advanced hemodynamic parameters. Previous therapeutic guidance of early-goal directed therapy (EGDT), which resuscitated based on the basic hemodynamics (central venous pressure and central venous oxygen saturation (ScvO2)) has lost its advantage compared with "usual care". Optimization of advanced hemodynamics, such as cardiac output and systemic vascular resistance, has now been endorsed as better therapeutic guidance for sepsis. Despite this, there are still some important hemodynamics associated with prognosis. In this article, we summarize the common techniques for hemodynamic monitoring, list important hemodynamic parameters related to outcomes, and update evidence-based therapeutic recommendations for optimizing resuscitation in pediatric septic shock.

Pediatric sepsis remains an important public health issue, and has similar incidence, morbidity, and mortality rates compared with critically ill adult populations [1]. Severe sepsis accounts for >8% of all critically ill children and causes >4.5 million childhood deaths worldwide annually [1,2]. In the United States, about one-third of deaths result from severe sepsis in pediatric intensive care units [1]. The majority of children suffering from sepsis die from refractory septic shock or multiple organ dysfunction syndrome with a high mortality rate ranging from 40 to 80% [3,4]. Death usually occurs within 72 h of initial resuscitation [5,6]. Severe sepsis can also result in serious health problems in children,

with an estimated cost of US$60,000 per patient, and a total annual cost of US$4.8 billion in the USA over the past decade [2].

Sepsis is defined as life-threatening organ dysfunction as a result of infection, while septic shock is defined as an infection that results in unstable hemodynamics and cardiovascular dysfunction (such as hypotension, use of vasoactive agents, impaired circulation) [7]. The dynamic changes and hemodynamics of septic shock are complicated and are associated with the pathophysiology. In sepsis, cardiovascular impairment results in tissue hypoperfusion which may deteriorate to multiple organ failure without appropriate treatment [8]. Therefore, understanding the pathophysiology of sepsis, early recognition, and maintenance of optimal hemodynamics to reverse tissue hypoperfusion, are very important for pediatric intensivists to improve the prognosis of pediatric sepsis.

Since 2001, early-goal directed therapy (EGDT) has been the recommended therapy for sepsis. EGDT resuscitation goals involve giving fluid based on the central venous pressure (CVP) level and giving vasoactive-inotropic agents to optimize mean artery pressure (MAP) and ScvO2 [9]. However, recently EGDT has not been recommended due to the lack of significant benefits reported by 3 randomized control trials (RCTs) [10−12]. Despite this, there are still many other hemodynamics which can be analyzed and measured, and can serve as resuscitation goals. Hemodynamic monitoring can also provide objective values for determining the severity of sepsis and monitoring the patient's response after resuscitation. However, there are many physiological variables and a growing range of medical equipment which can monitor these hemodynamic parameters in sepsis. In this study, we summarize the pathophysiology of septic shock and the recent practical aspects of hemodynamic monitoring as a guide for resuscitation in pediatric septic shock.

Pathophysiology of septic shock

The main pathophysiology of sepsis involves the infection activating host response, innate immunity, coagulation abnormalities, organ impairment, dysfunction of the vascular endothelium, anti-inflammatory mechanisms and immunosuppression [13]. The sepsis cascade affects hemodynamics by damaging the cardiovascular system. The causes of septic myocardial depression are multifactorial and involve genetic, molecular, metabolic and structural modifications with clinical features of global (systolic and diastolic) dysfunction [14]. Microvascular thrombosis caused by impairment of anticoagulant mechanisms, also called disseminated intravascular coagulation (DIC), is another major feature of sepsis [15]. Microvascular thrombus results in diminished oxygen delivery and tissue hypoperfusion. Damage of the vascular endothelium caused by inflammatory cytokines leads to loss of barrier function, giving rise to capillary leak, interstitial edema and decreased vasomotor tone [16]. In addition, inflammatory cytokines also result in mitochondrial oxidative stress damage and dysfunction [17]. In conclusion, DIC,

injured vascular endothelium and mitochondria all reduce tissue oxygenation, resulting in organ dysfunction.

Hemodynamic monitoring

In general, hemodynamics in sepsis can be divided into two groups: basic and advanced hemodynamic parameters. Basic hemodynamics encompass the common variables, which can be obtained in basic facility settings with less invasive methods, such as heart rate (HR), systolic blood pressure (SBP), mean artery pressure (MAP), central venous pressure (CVP), central venous oxygen saturation (ScvO2), perfusion pressure (MAP-CVP) and lactate.

Advanced hemodynamics refers to variables obtained by special instruments, that require in-depth interpretation, such as cardiac output (CO), cardiac contractility, preload, including intravascular volume and fluid responsiveness, and afterload, which can be evaluated by several different methods: Fick method (calorimetry and partial CO_2 rebreathing method), dilution methods (thermodilution, dye dilution), doppler techniques and bioimpedance.

Basic hemodynamic monitoring

HR and SBP
The presentation of shock varies, however the general signs are tachycardia and low blood pressure. Optimal HR and SBP for the patient's age should be one of the goals of resuscitation [18]. The shock index (SI), defined as the ratio of HR to SBP, is reported as a noninvasive method for grading hemodynamic stability and is a better parameter than HR or SBP alone for evaluating hemodynamic status in pediatric septic shock [19]. The SI can reflect vascular and myocardial impairment and is associated with tissue perfusion [20]. An SI >0.9 is associated with tissue hypoperfusion and increased mortality in adult patients [21]. In pediatric septic shock, an initial increased SI is also associated with an increased risk of mortality [19,22]. Age-specific SI cutoff values can identify those at higher risk of mortality in pediatric septic shock and the trend of SI enables enhanced targeted resuscitation [22], where those with increased SIs may benefit from more aggressive resuscitation. One prospective study identified the age-specific SI cutoff values for predicting early mortality in pediatric septic shock (1.98 for 1 month to <1 year; 1.5 for 1 to <6 year; 1.25 for 6−12 years) [22], (level of evidence: II; Table 1).

CVP and MAP-CVP
Initial resuscitation for pediatric septic shock was once aggressive fluid replacement guided by the CVP level [23]. However, during recent years, several studies have demonstrated that CVP level can only be a static marker of preload and is not reliable for intravascular volume status and preload responsiveness [24,25]. It was shown that using the CVP level as a therapeutic goal in EGDT may result in fluid overload [26,27]. Several studies in adult septic shock demonstrated that elevated CVP was associated with mortality [28,29] and one recent study reported that higher CVP (>12 mmHg) was associated with increasing mortality in pediatric septic shock [29]. Hence, CVP is no longer the priority goal of therapy, but

Table 1 Levels of evidence for prognostic studies.

Level	Type of evidence
I	High quality prospective cohort study with adequate power or systematic review of these studies
II	Lesser quality prospective cohort, retrospective cohort study, untreated controls from an RCT, or systematic review of these studies
III	Case-control study or systematic review of these studies
IV	Case series
V	Expert opinion; case report or clinical example; or evidence based on physiology, bench research or "first principles"
Levels of evidence for therapeutic studies	
1A	Systematic review (with homogeneity) of RCTs
1B	Individual RCT (with narrow confidence intervals)
1C	All or none study
2A	Systematic review (with homogeneity) of cohort studies
2B	Individual Cohort study (including low quality RCT, e.g. <80% follow-up)
2C	"Outcomes" research; Ecological studies
3A	Systematic review (with homogeneity) of case–control studies
3B	Individual Case-control study
4	Case series (and poor quality cohort and case–control study)
5	Expert opinion without explicit critical appraisal or based on physiology bench research or "first principles"

rather the aim is to optimize normal perfusion pressure (55 + age × 1.5, mmHg) to keep adequate renal and distal perfusion, and to increase tissue oxygenation [30]. Two pediatric studies demonstrated that therapeutic goals targeting normal perfusion pressure for age, were associated with better outcomes in children with septic shock [31,32] (level of evidence: 2B; Table 1).

ScvO2
ScvO2 is a hemodynamic measure representing the balance between oxygen delivery and consumption. Targeting ScvO2 >70% was once one of the core interventions of EGDT and one of the resuscitation endpoints in sepsis [9]. However, recent studies including 3 RCTs and one meta-analysis, reported that hemodynamic management based on EGDT did not lead to a better prognosis compared with the usual care without monitoring ScvO2 in adult septic shock [10–12,33]. In the pediatric group, only one small RCT analyzing 102 children with septic shock reported better outcomes in patient resuscitation targeting ScvO2 >70%, but no other high-quality studies have compared the outcomes between EGDT and usual care [31]. Therefore, targeting ScvO2 >70% was also recommended for pediatric sepsis but the original form of EGDT should be modified in the future (level of evidence: 2B; Table 1).

Lactate
Blood lactate levels were a quantifiable parameter associated with tissue hypoperfusion. In pediatric septic shock, elevated serum lactate levels were associated with poor prognosis [34], and early serum lactate levels >36 mg/dL ($\cong$ 4 mmol/L) were strongly associated with mortality [34]. The resuscitation goal of normal lactate levels (<2 mmol/L or 18 mg/dL) within 4 h in pediatric sepsis was associated with a decreased risk of organ dysfunction [35]. Furthermore, two studies demonstrated that lactate clearance was a predictor of mortality in pediatric septic shock; one study identified 24-h lactate clearance with a

threshold of 10% [36] and another study reported that 24-h lactate clearance was superior to 6-h and 12-h lactate clearance with a threshold of 20% [37]. In other words, increased lactate levels may reveal insufficient resuscitation, so additional therapeutic strategies to promote hemodynamic stability are required immediately. Therefore, the trend of lactate levels is recommended as a guide for resuscitation in pediatric sepsis [7] (level of evidence: I; Table 1).

Advanced hemodynamic monitoring

CO and cardiac index (CI)
CO is one of the most important dynamic parameters of advanced hemodynamics. CO, expressed in L/min, is the volume of blood pumped by the heart every minute and can be described using the equation: CO = stroke volume (SV) x HR. There are four important factors generating CO: HR, contractility, preload and afterload, and each of those factors is crucial for sepsis and septic shock. Since the calculation of CO is quite different between obese and lean individuals [38], for the convenience of clinical application, index hemodynamics are commonly accepted based on the body surface area (BSA). Therefore, CI, measured in L/min/m², is defined as: CO (L/min)/BSA (m²). Optimization of CI within the range of 3.5–5.5 L/min/m² was recommended by the Surviving Sepsis Campaign Guidelines (SSCG) in 2020 [7], and lower or higher CIs were associated with poorer outcomes [39] (level of evidence: 2A; Table 1).

SVRI
The systemic vascular resistance index (SVRI) represents cardiac afterload and is one of the clinical manifestations of sepsis pathophysiology [16]. The primary pathophysiology of early sepsis is injured endothelium resulting in peripheral vasodilatation combined with increasing CO (warm shock) [39,40]. Then the autonomic nervous system is activated after

sepsis and secreted circulating catecholamines also stimulate the initial inflammatory response [41]. Meanwhile, the subsequent evolution of hemodynamics may lead to an increasing SVRI and decreasing CO (cold shock) [39].

However, in critical conditions, the evolution of hemodynamics is quite different, such as fluid-refractory catecholamine-resistant septic shock, which has features of persistent vasodilatation, otherwise termed "vasoplegia". Vasoplegia means injured endothelium hyporesponsiveness to vasopressors resulting from desensitization and decreased expression of adrenoceptors on the surface of the endothelium [42]. Furthermore, vasoplegia only describes the static state of the vascular diameter in response to specific intraluminal and transmural pressures and may not reflect comprehensive dynamic hemodynamic data. Our team recently created the following formula: vascular reactivity index (VRI) = SVRI/VIS, to quantify the severity of vasoplegia and to provide dynamic data on the clinical progression of vasoplegia, and reported a favorable predictive power (average AUC >0.8) for mortality in children with vasoplegic septic shock [43] (Fig. 1). A lower VRI (VRI <30) indicates more severe vasoplegia and a higher risk of mortality in children with septic shock, and an immediate reevaluation should be performed to see whether there are other unnoticed factors, such as inappropriate antibiotics, worsening end-organ hypoperfusion, or uncontrolled infectious sources [43] (level of evidence: II; Table 1).

The 2020 SSCG recommended that optimal SVRI was within 800–1600 dyne-s/cm^5/m^2, and a lower or higher SVRI were associated with poorer outcomes [7] (level of evidence: 2A; Table 1). Furthermore, our study demonstrated that SVRI can serve as an earlier prognostic factor than CI for predicting mortality [44]. The lower the initial SVRI, the higher the mortality rate, and vasopressors (norepinephrine or epinephrine) should be used immediately to increase low SVRIs [7]. Conversely, if the SVRI increased to a high value, a lower CO may develop due to excessive afterload and myocardial restriction; vasoactive-inotropic agents should then be titrated based on the CI and SVRI.

Fluid responsiveness
Both hypovolemia and hypervolemia are associated with poor prognosis [45], and evaluation of volume status and fluid responsiveness are important for fluid management in sepsis. The standard method of evaluating fluid responsiveness is giving a fluid bolus then continuously monitoring the increase in CO [46]. Static hemodynamics, such as HR, SBP and CVP should not be used to guide fluid resuscitation as they are not a reliable measure of fluid responsiveness [24,25,47]. Several dynamic parameters (systolic pressure variation (SPV), pulse pressure variation (PPV), and stroke volume variation (SVV)) are valid markers for estimating fluid responsiveness in ventilated adults. However, dynamic parameters such as SPV, PPV, SVV and respiratory variations of inferior vena cava diameter (ΔIVCD) all reported poor predictive power for fluid responsiveness in ventilated children in two review studies [47,48].

SPV, PPV, SVV and ΔIVCD
SPV, PPV and SVV are parameters which are determined by analyzing the variation in arterial pressure waveforms, resulting from mechanically ventilated cycles. These parameters have been proven as valid hemodynamics for predicting fluid responsiveness in adult patients with sepsis [49,50]. However, arterial pressure-derived hemodynamics are poor predictors for evaluating fluid responsiveness in pediatric patients as reported in recent studies (all AUC <0.8) [47,51–55]. ΔIVCD is determined via an ultrasound to analyze the respiratory variations in vena cava inferior diameter. Many recent studies have demonstrated that ΔIVCD is not a reliable predictor of fluid responsiveness in the pediatric group [55–59].

The contradicting results for the ability of these hemodynamics to predict fluid responsiveness between adult and pediatric groups, may be due to the following reasons. First, the artery systems of children have a higher elasticity than adults [60]. Arterial pulse pressure is proportional to the stroke volume but conversely related to arterial elasticity. The variation in arterial blood pressure induced by ventilation is smaller in children with higher arterial elastic properties [60]. Second, children have higher chest wall and lung compliance than adults. The variation in intrathoracic pressure induced by ventilation is smaller in patients with higher respiratory compliance, which may not generate significant circulatory changes [47,48,61]. Third, children have lower cardiac ventricular compliance than adults, which correlated with less steep Frank-Staring curves, and resulted in less variation in stroke volume induced by ventilation [47].

Respiratory variation in aortic blood flow peak velocity (△Vpeak ao)
Two systemic reviews demonstrated that the △Vpeak ao, as measured by ultrasound, can be an accurate predictor of fluid responsiveness in ventilated children [47,62] (level of evidence: 1B; Table 1). △Vpeak ao was determined by a bedside ultrasound to measure the maximal and minimal values of aortic peak velocity over a single respiratory cycle and was

$$\textbf{SVRI} = 80 \text{ x (MAP − CVP) / CI}$$
$$\textbf{VIS} = \text{Dopamine dose (µg/kg/min) + Dobutamine dose (µg/kg/min) + 10 x Milrinone dose (µg/kg/min) + 100 x Epinephrine dose (µg/kg/min) + 100 x Norepinephrine dose (µg/kg/min) + 10,000 x Vasopressin dose (units/kg/min)}$$

Fig. 1 The equations of SVRI and VIS. Abbreviations used: SVRI: systemic vascular resistance index; MAP: mean arterial pressure; CVP: central venous pressure; CI: cardiac index; VIS: vasoactive-inotropic score.

defined as follows: (Vpeak ao max − Vpeak ao min)/[(Vpeak ao max + Vpeak ao min)/2]. The threshold value of △Vpeak for predicting fluid responsiveness in ventilated children were reported as ranging from 7 to 20% [47,55,61,62]. △Vpeak ao can be easily performed by ultrasonic cardiac output monitoring (USCOM).

The passive leg raising (PLR) test is a simple and effective method for evaluating fluid responsiveness with auto-transfusion of blood from the lower extremities. PLR has also been shown to be more predictive of fluid responsiveness than pulse pressure methods (SPV, PPV) in adults [63]. In children with either mechanically ventilated or spontaneous breathing, one study reported that PLR can predict fluid responsiveness which in the condition that a CI increase by ≧10% induced by PLR [64] (level of evidence: 2A; Table 1). In conclusion, △Vpeak ao and PLR are the two main methods that have a high predictive power for fluid responsiveness in children today.

Extravascular lung water index (EVLWI)

Extravascular lung water refers to the fluid in the alveolar and interstitial area. Increased extravascular lung water is associated with acute lung injury and a higher EVLWI (≧12 ml/kg) indicates clinical features of pulmonary edema in adults [65]. Also, in critically ill children, an elevated EVLWI correlates with increased pulmonary permeability and fluid overload [66]. In ventilated children, an EVLWI >10 ml/kg is significantly associated with a lower PaO_2/FiO_2 ratio, a higher oxygen index, and a higher mortality rate, while a lower EVLWI is significantly associated with survival [66]. Therefore, the EVLWI can be a reliable prognostic hemodynamic measure in critically ill children (level of evidence: II; Table 1).

Techniques for hemodynamics monitoring

Fick method

The Fick method is based on the principle that total uptake oxygen matches the product of CO and the arteriovenous oxygen difference. The Fick principle was the gold standard method for measuring CO and was defined as CO = oxygen consumption/arteriovenous oxygen difference. Although the technique is very accurate it is not practical for bedside use or continuous CO monitoring. The other disadvantage is that it requires an invasive procedure (pulmonary artery catheters) and must be performed under intubation, and errors occur when there are leaks in the endotracheal tube [67].

Noninvasive cardiac output (NICO) method

The NICO method is a modification of the Fick principle, which uses a partial CO_2-rebreathing method to measure CO (CO = change in CO_2 production/slope of CO_2 dissociation curve x ETCO2). Advantages of this method are that it is accurate and less invasive but it has the disadvantage of being performed under sedative in ventilated patients, and it may cause hypercapnia [68]. Furthermore, significant pulmonary disease, including ARDS, pneumonia, shunting, etc. will result in errors [68].

Dilution methods

Thermodilution with pulmonary artery catheter (PAC)

The PAC method was first used in 1970 by Swan-Ganz and was the standard method for measuring hemodynamics at the time. The PAC method involves a flow-directed catheter which is placed in the pulmonary artery, and hemodynamics are then measured by thermodilution. However, PAC has been used less recently due to its increased risk of complications, such as infections and thrombosis; in addition, the size of the catheter is not easy to use in small children [69]. Furthermore, the PAC method reports the right heart CO, which is not exactly the same as the left heart CO (if there is presence of an intracardiac or intrapulmonary shunt), and no significant benefit to therapy has been reported by the use of PAC compared with standard care without PAC [70].

Transpulmonary thermodilution methods

Pulse Contour Cardiac Output (PiCCO) uses a combination of two important methods to measure advanced hemodynamics: transpulmonary thermodilution and pulse contour analysis. The PiCCO system has been proven to be as accurate as the Fick principle for measuring CO and other hemodynamics, such as preload, afterload, extravascular lung water status and fluid responsiveness in the pediatric group, and has been widely used in seriously ill children worldwide [71]. An advantage of the PiCCO technique is that it is a less invasive procedure, and can provide continuous hemodynamic monitoring. However, disadvantages include the need for a specialized arterial line (commonly inserted in the femoral artery), a CVC (jugular or subclavian) and routine calibration with cold fluid administration (additional fluid load), and the fact that it is not applicable for arrhythmias and valvulopathies.

Pulse dye densitometry (PDD)

PDD is a method that estimates the indocyanine green concentration in an artery via a fingertip sensor after indocyanine green passage through the cardiopulmonary circulation. PDD has been proven as a rapid and available beside technique for evaluating CO in the pediatric group [72]. Advantages of PDD are that it is accurate, nontoxic, and less invasive but a disadvantage is that sequential measurements are limited by dye clearance.

Lithium dilution method (LiDCO)

The Lithium dilution method is less invasive and needs a venous and arterial catheter, then lithium chloride is injected via the venous catheter and measured by a sensor attached to the arterial catheter. The CO is measured from the lithium concentration−time curve via a pulse contour analysis system and has been proven to be effective in the pediatric group [73]. An advantage of this method is that it is

less invasive (a peripheral venous and peripheral arterial line) and accurate, but has the disadvantage of toxic effects with long-term lithium use.

Doppler CO monitoring methods

Transesophageal doppler (TED) and esophageal doppler (ED)

TED and ED are both performed using a flexible ultrasound probe that is placed in the distal esophagus and measures the Doppler flow in the descending aorta. The CO is calculated from the product of the aortic root cross-sectional area (CSA), the stroke distance within the descending aorta (=velocity-time integral, VTI), and HR. The difference between TED and ED is that TED requires manipulation of the probe until the optimal VTI is found, while ED only needs the probe to be placed in the esophagus in front of the descending aorta. ED uses a pediatric nomogram based on the child's age, weight and height to determine the aortic diameter, instead of direct measuring of the CSA. TED and ED are proven to accurately estimate CO in the pediatric group [74]. This method may cause some bias in the pediatric group because the observer is blinded to the probe placement and this may result in variability in the mean aortic flow velocities. Without direct measuring, the CSA may also cause a bias when using ED [74].

Transcutaneous doppler

Transthoracic echocardiography (TTE) is the most commonly used echocardiogram where the probe is placed on the chest. TTE can evaluate blood flow velocity in the left ventricular outflow tract (LVOT) and right ventricular outflow tract (RVOT) to calculate CO. TTE has the advantages of being low cost, low risk, and available as a beside technique for evaluating CO in the pediatric group [75].

USCOM is a non-invasive technique for measuring CO via continuous-wave Doppler ultrasound. The transducer is placed in the suprasternal notch and the left parasternal position to measure the blood flow velocity through the aortic and pulmonary valves. Then the monitor will display the time velocity curve, and the CO value is calculated using the flow integral. USCOM has the advantage of a short learning curve, and has accuracy comparable with PAC for evaluating CO in the pediatric group [76].

In conclusion, although all Doppler CO monitoring methods are relatively non-invasive and available for bedside use, these methods must be used with caution. For example, when the Doppler measures the flow of the descending aorta, we assume a regular proportion of flow between the left ventricular flow and the descending aorta. However, the proportion may change in hemodynamically unstable patients. In addition, the CSA of the aortic root is not fixed, and using the aortic diameter from the pediatric nomogram may lead to erroneous results. Furthermore, all ultrasonic techniques are operator dependent, which may lead to a degree of inter- and intra-observer variability.

Thoracic electrical bioimpedance (TEB)

There are 2 basic technologies for TEB: Impedance cardiography (ICG) and Electrical Cardiometry (EC). Both ICG and EC are non-invasive techniques measuring electrical conductivity of the thorax and timing its variation produces continuous hemodynamics, such as CO, SV, SVV and SVRI. The ICG method mainly detects the rapid change in bioimpedance to volumetric expansion of the aorta, while the EC detects the change in the direction of erythrocytes and the peak velocity in the ascending aorta. Both the ICG and EC techniques have good agreement with Doppler CO monitoring methods in pediatric groups [77,78]. A disadvantage of these techniques is that they are not precise in patients with varying intrathoracic fluid content or vascular resistance.

Hemodynamic management of patients with septic shock

Fluid management

Initial volume expansion with 10−20 ml/kg aliquots per bolus (up to 40−60 ml/kg within 1 h) with frequent assessment of hemodynamics (mainly CO) was recommended as first-line management in children with septic shock [7]. Clinical markers for considering fluid bolus included HR, BP, urine output, and blood lactate. Clinical signs of overdosed fluid included new onset acute pulmonary edema and hepatomegaly, which indicated that fluid bolus was no longer recommended. Overdosed fluid is associated with poor prognosis in both adult and pediatric septic shock [27−29]. Administering fluid bolus based on available monitoring techniques for evaluating fluid responsiveness can reduce the chance of fluid overload [47,61]. Fluids can be considered in the same ways as drugs and must be carefully administrated to patients in a reasoned way based on reliable hemodynamics.

Several types of fluid, including crystalloids (normal saline or lactated Ringer's solution), colloids (albumin, hydroxyethyl starch (HES), or gelatin) and blood products were analyzed for the resuscitation of patients with sepsis. Crystalloids are preferred over colloids for resuscitation in patients with sepsis as they are less expensive and have less adverse effects. One RCT including 3141 septic children reported no clear benefits from albumin administration [79], and one RCT which compared gelatin-derived fluid with normal saline reported no additional benefits [80]. Despite no study comparing HES with other available fluids for resuscitating pediatric septic shock, the use of HES as a resuscitating fluid was analyzed in one meta-analysis, which reported an increased risk of acute kidney injury (AKI), and mortality in adults with septic shock [81]. Therefore, crystalloids are recommended as the first-line volume expander in pediatric septic shock [7,30] (level of evidence: 2A; Table 1). Furthermore, normal saline was associated with more side effects, such as hyperchloremic acidosis, AKI, and mortality compared with lactated Ringer's (balanced crystalloids) in one RCT of adult septic shock [82]. Two pediatric studies also reported similar benefits for lactated Ringer's compared with normal saline in children with septic shock [83,84]. Although no high-quality pediatric research has been conducted, lactated Ringer's is preferred over normal saline as the first-line volume expander in pediatric septic shock and was recommended in 2020 by the SSCGs [7] (level of evidence: 2A; Table 1). Normal saline can be used if lactated Ringer's is not available or under certain special conditions, such as hyponatremia or when increased intracranial pressure is suspected [7].

Cardiovascular drug therapy

The hemodynamics of sepsis evolve dynamically and the cardiovascular drug should be adjusted over time to maintain optimal hemodynamics and adequate organ perfusion. Frequent monitoring of the hemodynamics is required while vasopressors are administered, especially in relation to CI, SVRI, and peripheral perfusion, to determine the proper combination of inotropes or vasodilators [7]. Administration of vasoactive agents is recommended after 40−60 ml/kg of fluid resuscitation or signs of fluid overload have been noticed while the patient is still having persistent symptoms of organ hypoperfusion [7].

Epinephrine and norepinephrine

Epinephrine has inotropic ($\leq$0.3 μg/kg/min, beta adrenergic inotropic effect dominates) and vasoactive effects (>0.3 μg/kg/min, alpha-adrenergic vasoconstrictive effect dominates); norepinephrine mainly has alpha-adrenergic vasoconstrictive effects and minimal beta adrenergic inotropic effects; they are both recommended by the 2020 SSCGs as first-line vasoactive-inotropic agents for treating pediatric septic shock based on two RCTs in children (recommended dose ranging from 0.1 to 0.3 μg/kg/min) [85,86] (level of evidence: 1B; Table 1). Furthermore, epinephrine is preferable for resuscitating myocardial impairment and low CI (mostly cold shock) while norepinephrine is preferable for patients with lower SVRI (mostly warm shock) [7].

Dopamine

Dopamine was endorsed as a first-line vasoactive-inotropic agent for pediatric septic shock in the 2012 SCCM guidelines [87]. Previous literature reported that dopamine had 3 effects on hemodynamics based on the dose range. Low dosage (1−5 μg/kg/min, dopaminergic receptor effect dominates) could increase renal function and urine output; intermediate dosage (5−10 μg/kg/min, beta adrenergic receptor effect dominates) could increase cardiac contractility and output; high dosage (>10 μg/kg/min, alpha-adrenergic receptor effect dominates) could cause vasoconstriction resulting in elevated SVR [88]. However, a RCT in adults and a systemic review in children both reported inconclusive findings for the effect of low-dose dopamine on improving renal function [89]. Furthermore, dopamine was replaced by epinephrine as the first-line vasoactive-inotropic agent for the management of pediatric septic shock because epinephrine is associated with a better prognosis compared with dopamine [85,86]. Therefore, dopamine is recommended only when epinephrine is not available for pediatric septic shock [7].

Inodilators (dobutamine, milrinone, levosimendan)

Dobutamine and milrinone are the two inodilators most often used in pediatric septic shock. Dobutamine mainly has beta adrenergic receptor effects at low doses and alpha adrenergic receptor effects at high doses. One study reported that a dose <7.5 μg/kg/min mainly increases CO and decreases SVR (beta adrenergic receptor effect). Doses ranging from 5 to 20 μg/kg/min may increase CO and SVR (alpha-adrenergic receptor effect) [90] (level of evidence: 3B; Table 1). Milrinone is a phosphodiesterase 3 inhibitor, which can improve cardiac contractility, increase lusitropic function (improve diastolic relaxation), and decrease SVR with afterload reduction. The common loading dose was 50 μg/kg/min administered over 10−60 min, followed by an infusion dose which ranged from 0.25 to 0.75 μg/kg/min. A recent study demonstrated that milrinone had anti-inflammatory properties on animals with endotoxemia caused by sepsis and could improve microcirculation, thereby improving survival [91]. Two studies reported that milrinone could improve blood pressure, CO and microcirculation in children with sepsis [92,93] (level of evidence: 2B; Table 1). Levosimendan is a calcium-sensitizing agent which can prevent low cardiac output syndrome in pediatric patients after open heart surgery potentially. Although the evidence for using inodilators in pediatric septic shock is weak due to the lack of RCTs, inodilators can still be considered as adjunctive agents for pediatric septic patients with a low CO and a high SVR [7]. However, clinicians must pay attention to the side effects of these inodilators. Dobutamine may cause an increased HR, ventricular arrhythmia, and hypotension. Milrinone may cause arrhythmia, hypotension and headaches. Levosimendan may cause arrhythmia, hypotension, hypocalcemia, anemia and gastrointestinal disorders.

Vasopressin-receptor agonists (vasopressin and terlipressin)

Vasopressin and terlipressin are both strong vasoconstrictors and may be considered for use in septic children with persistent hypotension despite high doses of epinephrine and norepinephrine [7]. Previous studies reported that vasopressin and terlipressin can improve blood pressure in vasodilated pediatric septic shock but decreased CO is a side effect and there is the potential for distal necrosis; furthermore, they have not been shown to be beneficial for improving survival [94,95].

Corticosteroids

Corticosteroids are not recommended for routine use in pediatric septic shock. However, some critical cases may lead to conditions in which corticosteroids could be beneficial, for example, in patients with absolute or relative adrenal insufficiency and vasoplegic shock. A benefit of corticosteroid administration in septic patients is that they restore balance to the altered hypothalamic pituitary adrenal axis. With regards to the cardiovascular system, corticosteroids can inhibit the secretion of endogenous nitric oxide and prostacyclin, and reverse the phenomenon of vascular hyporesponsiveness to vasopressors [42], modulate capillary leak syndrome, stimulate calcium availability in myocardial cells [96], and improve cardiac contractility and vasoconstriction. Side effects after corticosteroid administration include an increased risk of hospital-acquired infections, worsening neuromuscular weakness and hyperglycemia [7,97]. A recent meta-analysis study demonstrated that corticosteroids could promote resolution of shock [98], however other recent studies have reported controversial effects of corticosteroids
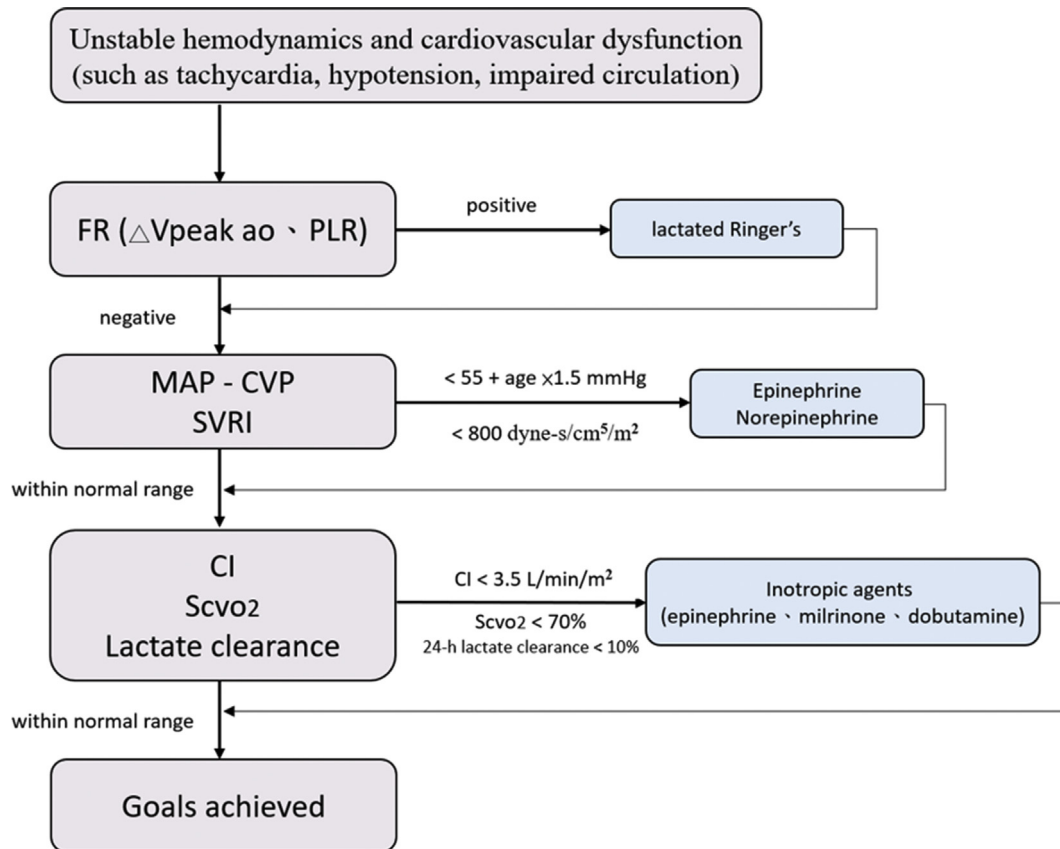
Fig. 2 Modified early-goal directed therapy algorithm. We modified the early-goal directed therapy algorithm based on new concepts and updated data. CVP (the static intravascular volume or preload) is replaced by fluid responsiveness. Preferred resuscitation fluid is lactated Ringer's solution. MAP (afterload) is replaced by perfusion pressure (MAP-CVP) or SVRI. The preferred vasoactive drugs for children are epinephrine or norepinephrine. In addition to Scvo2, CI < 3.5 L/min/m² and lactate clearance are used to represent inadequate cardiac output in children. Milrinone, though not widely used in adult patients, is one of the drugs that may improve microcirculation for children. Abbreviations used: FR: fluid responsiveness; △Vpeak ao: Respiratory variation in aortic blood flow peak velocity; PLR: passive leg raising; MAP: mean artery pressure; CVP: central venous pressure; SVRI: systemic vascular resistance index; CI: cardiac index; ScvO2: central venous oxygen saturation.

being associated with mortality [98,99]. Further high-quality RCTs are warranted to evaluate the potential risks and benefits of corticosteroids for pediatric septic shock.

Extracorporeal life support (ECLS)

ECLS is recommended as the last resort for hemodynamic management of pediatric refractory septic shock because of the potential complications, such as hemorrhage and thromboembolic events. To date, no RCTs have evaluated the effects of ECLS on prognosis in pediatric septic shock. A recent study used propensity score matching to analyze a relatively large number of children with refractory septic shock (44 children receiving ECLS, 120 children receiving conventional therapy), and reported no significant difference in survival between the two groups [100]. ECLS is only considered in pediatric septic shock which is refractory to all other advanced resuscitations.

Summary

Early recognition, resuscitation and initial management of pediatric septic shock can improve outcomes. When septic shock is recognized, crystalloid challenge is recommended after a rapid evaluation of the basic hemodynamics, such as the HR, SBP, CVP level, MAP-CVP, ScvO2 and lactate level. Evaluation of advanced hemodynamics is suggested in critical conditions, such as persistent hypotension despite initial crystalloid volume expansion. Assessment of fluid responsiveness should be conducted to decide whether or not to continue volume expansion. Then vasoactive-inotropic agents should be administered based on the CI and SVRI hemodynamics. Clinicians should monitor the dynamic changes in these hemodynamic parameters continuously until they are optimized. Because recent studies report that hemodynamic management based on EGDT did not lead to a better

prognosis and has lost its advantage. For clinical practice, we summarize the latest hemodynamic studies associated with prognosis and recommend a modified EGDT algorithm (Fig. 2) based on the most recent knowledge.

Conflicts of interest

The authors declare no conflicts of interest.

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