

# Pediatric Sepsis: Clinical Considerations

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## Abstract

Sepsis remains one of the leading causes of childhood mortality today, although survival has substantially improved, thanks to an ever deeper and more thorough understanding of sepsis pathophysiology, developments in vaccination and intensive therapy, and goal-directed therapeutic approaches. The key to successful therapy is early recognition and antibiotic treatment, as well as supportive therapy aimed at correcting circulatory, respiratory, and metabolic derangements as soon as possible. Diagnosis and management of childhood sepsis mainly evolves along the path of studies conducted in adult patients; however, their applicability is limited due to a variability of cardiovascular and immune responses in each age group. In addition to childhood characteristics of hemodynamic responses in sepsis, this review looks at major areas of pediatric sepsis therapy, with the intention of providing bedside clinicians with pointers useful in their day-to-day work.

## Keywords

- ▶ sepsis
- ▶ septic shock
- ▶ children
- ▶ pediatric
- ▶ infection
- ▶ review

## Introduction

Sepsis is a systemic inflammatory response syndrome (SIRS) triggered by a suspected or verified pathogen or its product;<sup>1</sup> our understanding of its pathomechanism has been on the rise.<sup>2,3</sup> The septic process is an extremely complex, simultaneous interplay of proinflammatory and anti-inflammatory responses.<sup>4–6</sup> The direction, extent, and magnitude of the host response are determined, on the one hand, by patient-specific factors (e.g., genetic predisposition, age, vaccination status, comorbidity, severe injury, medication taken, use of invasive equipment) and, on the other hand, by virulence factors of the pathogen (mostly bacteria, also viruses, fungi, parasites).<sup>7–9</sup> The disease process has an effect on practically all organ systems; sepsis is often accompanied by the disruption of cardiovascular function, intravascular volume status, respiratory function, immune/inflammatory regulation, renal function, coagulation, and hepatic function.<sup>10</sup> Childhood sepsis is a global health problem, with incidence

and outcomes varying across regions.<sup>11</sup> Sepsis is one of the leading causes of death in children;<sup>12</sup> its mortality is between 2 and 10%,<sup>13–15</sup> which is much lower than in adults.<sup>16</sup> Hospital mortality in the United States was found to be 2% in healthy children, and 8% in patients suffering from chronic diseases.<sup>12</sup> For more than two-thirds of the cases, airway or bloodstream infections are identified in the background.<sup>11,17,18</sup> The most vulnerable pediatric groups include preterm newborns, infants, sufferers from hereditary or acquired immune deficiencies, chronic debilitating medical conditions, severe trauma victims, and those recovering from major surgery or implanted with invasive medical equipment.<sup>19,20</sup> Early detection and adequate first line treatment are essential: every single hour spent in hypotension and with capillary refill longer than 3 seconds doubles the chance of mortality.<sup>21</sup> Thanks to a therapeutic strategy that emphasizes early diagnosis, aggressive fluid therapy, and vasoactive support, as well antibiotic treatment as early as possible, the mortality of childhood sepsis is gradually

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decreasing;<sup>22</sup> however, a growing number of children with predisposing comorbidities and a rise in sepsis prevalence due to the spread of multidrug resistant pathogens continue to challenge health care providers worldwide.<sup>11</sup> The objective of this review is to provide a summary of the clinical management of childhood sepsis and septic shock.

## Diagnosis

Historically, the term *sepsis* was widely used in relation to a diverse group of syndromes, which often confused clinicians.<sup>23</sup> In 1992, as part of standardization efforts for the definition, the American College of Chest Physicians and the Society of Critical Care Medicine introduced the term *systemic inflammatory response syndrome*, defined as a widespread inflammatory response that may or may not be associated with infection.<sup>24</sup> In 2005, the International Pediatric Consensus Conference adapted the definitions of SIRS, sepsis, and other related terms (► **Tables 1–2**) to pediatric age groups (► **Table 3**) by introducing age-specific heart rate, respiratory rate, and white blood cell count cutoffs (► **Table 4**). In addition to facilitating observational study design and the assessment of various therapeutic interventions in clinical trials, this set of distinct definitions (sepsis, severe sepsis and septic shock, organ failure) serves as a guide to clinicians in severity assessment, progression monitoring, and treatment response evaluation.<sup>25,26</sup> However, it is important to note that the diagnosis of childhood sepsis should not be confined to a predefined set of pathophysiological and laboratory deviations: in an observational study at an academic medical center, only two-thirds of patients under the age of 18 years treated for sepsis or septic shock

satisfied the strict requirements of the consensus system of criteria.<sup>27</sup> Lately, more and more clinicians question the usefulness of SIRS criteria in sepsis and call for separate sets of definitions for clinical versus research use.<sup>28,29</sup> In February 2016, new definitions and clinical criteria of adult sepsis and septic shock were introduced at the 45th Annual Critical Care Congress.<sup>30</sup>

Medical conditions elicited by any sort of proven or presumed pathogens are defined as infections. Infection can be confirmed by positive bacterial culture, tissue stain, or polymerase chain reaction (PCR) test. Infection is presumable in certain clinical syndromes (e.g., fever and coughing, appearance of petechiae and purpurae accompanied by hemodynamic instability, meningism, abscess, organ perforation); it should also be suspected when consistent with laboratory or imaging findings (e.g., pulmonary infiltration on chest X-ray, presence of leukocytes in normally sterile body fluids).<sup>1</sup>

In a great majority of sepsis cases, the site of infection is likely to be identified through medical history, physical examination, laboratory tests, and various imaging studies. To identify the pathogen, it is recommended to collect two peripheral blood cultures (both aerobic and anaerobic) prior to treatment, and an additional sample from any intravascular tubes in place for more than 48 hours.<sup>31–33</sup> The positive predictive value of testing can be improved, and contamination rates reduced, through proper sampling of at least 1 mL or, for older children, 3–10 mL of blood<sup>33–36</sup> by a trained phlebotomist or experienced blood culture team<sup>37–39</sup> using sterile latex gloves and best-practice antisepsis.<sup>40</sup> In an effort to not cause pain or more discomfort, pediatricians often use intravenous catheters for blood culture sampling;<sup>41</sup> however,

**Table 1** Definitions of SIRS, infection, sepsis, severe sepsis, and septic shock

SIRS	The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:
	Core temperature of >38.5°C or <36°C
	Tachycardia, defined as a mean heart rate >2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5- to 4-h period or for children <1 y old: bradycardia, defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, beta-blocker drugs, or congenital heart disease; or otherwise unexplained persistent depression over a 0.5-h time period
	Mean respiratory rate >2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia
	Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or >10% immature neutrophils
Infection	A suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen or a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical exam, imaging, or laboratory tests (e.g., white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans)
Sepsis	SIRS in the presence of or as a result of suspected or proven infection
Severe sepsis	Sepsis plus one of the following: cardiovascular organ dysfunction or acute respiratory distress syndrome or two or more other organ dysfunctions; organ dysfunctions are defined in ► <b>Table 2</b>
Septic shock	Sepsis and cardiovascular organ dysfunction as defined in ► <b>Table 2</b>

Abbreviations: SD, standard deviation; SIRS, systemic inflammatory response syndrome.  
Source: Data from Goldstein et al.<sup>1</sup>

**Table 2** Organ dysfunction criteria

Cardiovascular dysfunction	Despite administration of isotonic intravenous fluid bolus $\geq 40$ mL/kg in 1 h:
	Decrease in BP (hypotension) 5th percentile for age or systolic BP $< 2$ SD below normal for age
	or
	Need for vasoactive drug to maintain BP in normal range (dopamine $> 5$ $\mu$ g/kg/min or dobutamine, epinephrine, or norepinephrine at any dose)
	or two of the following
	Unexplained metabolic acidosis: base deficit $> 5$ mEq/L
	Increased arterial lactate more than two times upper limit of normal
	Oliguria: urine output $< 0.5$ mL/kg/h
	Prolonged capillary refill: $> 5$ s
Core to peripheral temperature gap $> 3^{\circ}\text{C}$	
Respiratory	PaO <sub>2</sub> /FiO <sub>2</sub> $< 300$ in the absence of cyanotic heart disease or preexisting lung disease
	or
	PaCO <sub>2</sub> $> 65$ Torr or 20 mm Hg over baseline PaCO <sub>2</sub>
	or
	Proven need or $> 50\%$ FiO <sub>2</sub> to maintain saturation $> 92\%$
	or
Need for nonelective invasive or noninvasive mechanical ventilation	
Neurologic	Glasgow Coma Score 11
	or
	Acute change in mental status with a decrease in Glasgow Coma Score $\geq 3$ points from abnormal baseline
Hematological	Platelet count of 80,000/mm <sup>3</sup> or a decline of 50% in platelet count from highest value recorded over the past 3 d (for chronic hematology/oncology patients)
	or
	International normalized ratio $> 2$
Renal	Serum creatinine more than two times upper limit of normal for age or twofold increase in baseline creatinine
Hepatic	Total bilirubin $< 4$ mg/dL (not applicable for newborn)
	or
	ALT two times upper limit of normal for age

Abbreviations: ALT, alanine aminotransferase; BP, blood pressure; SD, standard deviation.  
Source: Data from Goldstein et al.<sup>1</sup>

avoiding this practice might significantly reduce the number of false-positive blood cultures.<sup>42</sup> Sampling should include other cultures (e.g., urine, wound exudate, airway secretions, cerebrospinal fluid) as appropriate for the primary infection site.<sup>16</sup>

Culture growth becomes apparent within a few days; however, a negative result can only be confirmed after 5 days.<sup>43,44</sup> In addition to time issues, another major limiting

**Table 3** Pediatric age groups for severe sepsis definitions

Newborn	0 d to 1 wk
Neonate	1 wk to 1 mo
Infant	1 mo to 1 y
Toddler and preschool	2–5 y
School age child	6–12 y
Adolescent and young adult	13 to $< 18$ y

Source: Data from Goldstein et al.<sup>1</sup>

factor of the technique is low sensitivity, which can be aggravated by prior antibiotic treatment and, especially with pediatric patients, sample volume limitations.<sup>45</sup> Challenges posed by growth-inhibiting bacteriostatic substances, low pathogen concentrations, and long incubation times of methods with high detection thresholds can be overcome using molecular amplification techniques.<sup>46–48</sup> PCR assays capable of detecting up to 25 types of bacteria and fungi within 4 to 6 hours are available today;<sup>49–53</sup> their application may open new dimensions in sensitivity and speed, providing treatment targets at early stages of life-threatening infections.

### Developmental Differences in the Hemodynamic Response to Sepsis in Children and Adults

One of the major challenges of pediatric critical care medicine is dealing with developmental differences that greatly

**Table 4** Age-specific vital signs and laboratory variables<sup>a</sup>

Age group	Heart rate (beats/min)		Respiratory rate (breaths/min)	Leukocyte count (leukocytes 10 <sup>3</sup> /mm <sup>3</sup> )	Systolic blood pressure (mm Hg)
	Tachycardia	Bradycardia			
0 d to 1 wk	>180	<100	>50	>34	<65
1 wk to 1 mo	>180	<100	>40	>19.5 or <5	<75
1 mo to 1 y	>180	<90	>34	>17.5 or <5	<100
2–5 y	>140	NA	>22	>15.5 or <6	<94
6–12 y	>130	NA	>18	>13.5 or <4.5	<105
13 to <18 y	>110	NA	>14	>11 or <4.5	<117

<sup>a</sup>Lower values for heart rate, leukocyte count, and systolic blood pressure are for the fifth and upper values for heart rate, respiration rate, or leukocyte count for the 95th percentile.

Source: Data from Goldstein et al.<sup>1</sup>

impact the pathophysiology of sepsis.<sup>7</sup> Age-related changes in heart rate, stroke volume (SV), blood pressure, systemic vascular resistance (SVR), hemoglobin concentration, metabolic rate, glycogen stores, and protein mass all contribute to differences in disease progress between children and adults and to the heterogeneity of cardiovascular and metabolic responses across pediatric age groups.<sup>7,10,54,55</sup> An essential requirement for successful treatment of childhood sepsis is the awareness of developmental differences and understanding of their effects on the function of various organ systems.

In septic shock, adult hemodynamic response is initially characterized by hyperdynamic (high-output) physiology, including low SVR, tachycardia, and normal or increased cardiac output (CO), as manifested by flash capillary refill, bounding pulses, warm and dry extremities, and wide pulse pressures (“warm” shock).<sup>56</sup> Myocardial dysfunction and reduced CO are compensated in adults through two mechanisms: elevation of heart rate and reduction of SVR.<sup>7,54,55,57</sup> In the absence of adequate intervention, progressive SVR reduction might result in maldistribution of CO and organ hypoperfusion. It is a sign of poor prognosis when compensation fails or is insufficient; the risk of death is also higher in patients whose SVR reduction does not respond to vasopressors.<sup>56,58,59</sup> Pediatric septic shock is often accompanied by hypovolemia; children therefore respond well to aggressive fluid therapy.<sup>55,57</sup> In contrast with the high-CO, low-SVR adult response, children’s pathophysiology is dominated by increased SVR and myocardial dysfunction.<sup>60–62</sup> Children’s cardiac reserves are limited. While adults tolerate even doubling of the resting heart rate to offset a decreased SV and maintain a sufficient CO fairly well, children do not have heart rate reserves for a similar increase. Although tachycardia is an important compensatory mechanism in children as well, the younger the patient, the more likely it is for the response to become inadequate with a critical heart rate increase; with the shortening of diastolic filling time and a consequential decrease of coronary perfusion, CO may continue to decline.<sup>10,55</sup> In addition to tachycardia, newborns, infants, and children maintain blood pressure by increasing SVR; in this case, clinical appearance is characterized by

hypodynamic physiology with tachycardia, delayed capillary refill, diminished pulses, cold and mottled extremities (“cold” shock).<sup>10,55,57</sup> Because vasoconstriction intensifies, hypotension comes as a late-onset sign in childhood septic shock;<sup>61</sup> however, in lack of adequate intervention, further increase in SVR becomes counterproductive as the disease progresses since, combined with increased afterload, it may lead to further reduction in CO, which, in turn, may cause septic shock decompensation, cardiac failure, and death.<sup>55</sup> Ceneviva et al classified 50 children with fluid- and dopamine-resistant septic shock on hemodynamic data acquired through a pulmonary artery catheter. Most of the examined patients (58%) was hypodynamic (low CO, high SVR), 20% showed a hyperdynamic response similar to that of adults (high CO, low SVR), whereas 22% was detected with a combination of low CO and low SVR. Four children showed a complete change in hemodynamic status.<sup>61</sup> In summary, contrary to adults, children produce a hypodynamic response to septic shock more often; in addition, their hemodynamic response as a whole is often heterogeneous and changes frequently with progress of the disease.

## Management of Sepsis in Children

Apart from antimicrobial therapy, management of sepsis is almost exclusively limited to supportive therapeutic interventions. The goal-directed approach to septic shock treatment emphasizes rapid restoration of vascular functions, oxygen delivery, and a therapeutic strategy aimed at early start antibiotics. Initial resuscitation endpoints should be reached as soon as possible, preferably within an hour (→ **Table 5**).<sup>16,21,57,63–67</sup> In therapy-resistant shock, constant advanced hemodynamic monitoring is essential in an intensive care setting. Numerous alternative approaches exist (SVR, SVR index, SV variation, global end-diastolic volume), but to date, only measurement of CO and venous oximetry have been adequately validated and incorporated in clinical guidelines.<sup>68–76</sup> Therapeutic interventions of hemodynamic support should be directed at maintaining mixed venous oxygen saturation at  $\geq 70\%$ , cardiac index between 3.3 and 6 L/minute/m<sup>2</sup>, and a normal perfusion pressure for age.<sup>16,57</sup>

**Table 5** Therapeutic goals during management of children with septic shock

Initial therapeutic endpoints:
<ul style="list-style-type: none"> <li>• Threshold heart rate associated with increased mortality in critically ill (not necessarily septic) infants are a HR &lt; 90 bpm or &gt; 160 bpm, and in children are a HR &lt; 70 bpm or &gt;150 bpm)</li> </ul>
<ul style="list-style-type: none"> <li>• Capillary refill time &lt; 2 s</li> </ul>
<ul style="list-style-type: none"> <li>• Strong distal pulses equal to central pulses</li> </ul>
<ul style="list-style-type: none"> <li>• Warm extremities</li> </ul>
<ul style="list-style-type: none"> <li>• Normal blood pressure for age</li> </ul>
<ul style="list-style-type: none"> <li>• Normal mental status</li> </ul>
<ul style="list-style-type: none"> <li>• Urine output &gt;1 mL/kg/h once effective circulating volume is restored</li> </ul>
<ul style="list-style-type: none"> <li>• Lactate &lt; 4 mmol/L or <math>\geq 10\%</math> decrease per every 1–2 h</li> </ul>
Central venous oxygen saturation greater than or equal to 70%
Cardiac index between 3.3 and 6 L/min/m <sup>2</sup>

Abbreviations: HR, heart rate.

Source: Data from Brierley et al.<sup>57</sup>

### Airway Management and Respiratory Support

In septic children, airways and respiration are to be closely observed since lung compliance and work of breathing might change rapidly and acute lung injury/acute respiratory distress syndrome (ALI/ARDS) are common complications.<sup>77</sup> Respiratory alkalosis of central origin is often detected in early stage sepsis. With the progress of the disease, metabolic acidosis, itself a consequence of progressive peripheral circulatory failure, may further deteriorate owing to respiratory acidosis caused by a consequential disturbance of consciousness and possible pulmonary complications.<sup>57</sup> Due to their generally lower functional residual capacity (FRC) and limited compensation reserves, septic children, especially young infants, may require endotracheal intubation even in early stage disease.<sup>16</sup> Respiratory muscles can demand up to 40% of the total CO<sub>2</sub>; this can be decreased for the benefit of vital organs through adequate oxygen therapy, respiratory support and ventilation, or administration of muscle relaxants;<sup>57</sup> however, increased intrathoracic pressure caused by invasive ventilation might lead to further deterioration by impeding venous return, especially if fluid status of the patient has not been stabilized prior to the intervention.<sup>16</sup>

Upon detection of respiratory distress in pediatric sepsis, and for all children with septic shock, 100% oxygen must be promptly given to improve peripheral oxygen delivery, with oxygenation constantly monitored by pulse oximetry.<sup>78</sup> In children receiving any oxygen therapy, once peripheral circulation has been restored and pulse oximetry is reliable, hyperoxia should be avoided to prevent potential harm caused by the production of free radicals.<sup>79</sup> In children, especially infants, whose normal oxygenation cannot be maintained by oxygen supply, nasal continuous positive airway pressure can be applied to increase FRC and reduce

work of breathing<sup>80</sup> or, as appropriate, bag-valve-mask ventilation should be used while securing venous access before endotracheal intubation and also during volume resuscitation and peripheral inotropic treatment.<sup>16,81</sup>

Judgment on the indication for endotracheal intubation should primarily consider age-specific respiratory rate, work of breathing, and level of consciousness; situations that may require intubation include ARDS, consciousness disorder, increased intracranial pressure, convulsion persisting after repeated benzodiazepine administration, central line insertion procedures, invasive hemodynamic monitoring, and metabolic acidosis expected to respond to slight mechanical hyperventilation.<sup>16,57,81</sup>

Mechanical ventilation can be life-saving, but low lung compliance and/or high peak pressures might lead to ventilator-induced lung injury through alveolar overstretching (volutrauma), repeated alveolar collapse–expansion cycles (atelectrauma), and oxygen toxicity.<sup>82</sup> During ventilation, lung protective strategies established in adult practice should be followed.<sup>16</sup> In sepsis accompanied by ALI/ARDS, FiO<sub>2</sub> and positive end expiratory pressure should be titrated for SpO<sub>2</sub> to be above 90%,<sup>83</sup> while still avoiding hyperoxia for reasons outlined previously. Similar to adult recommendations, pH should be maintained within the range of 7.3 to 7.45; in certain cases, permissive hypercapnia might be advantageous unless contraindicated.<sup>84,85</sup> Optimal peak pressure is below 30 cm H<sub>2</sub>O; the recommended tidal volume is 4 to 6 mL/kg, with values above 10 mL/kg avoided.<sup>16,83,84,86</sup> In case conventional ventilation fails, high-frequency oscillatory ventilation can be applied as rescue treatment.<sup>87–89</sup>

### Sedoanalgesia

In the treatment of septic children, sedoanalgesia might be necessary during endotracheal intubation, mechanical ventilation, invasive interventions (e.g., securing a central line), and hemodynamic monitoring. Aggressive fluid and vasoactive therapy for early stabilization significantly decreases the risk of hemodynamic collapse during intubation.<sup>90</sup> Introduction and maintenance of sedoanalgesia requires attention to vasodilatory, direct myocardial depressive, and endogenous catecholamine suppressor effects of candidate substances (propofol, thiopental, benzodiazepines, opioids) because these might cause a deterioration of the patient's cardiovascular status.<sup>57</sup> Etomidate inhibits 11- $\beta$ -hydroxylase, an enzyme involved in adrenal steroid hormone synthesis, in a concentration-dependent and reversible manner.<sup>91,92</sup> A single dose alone can cause adrenal suppression lasting beyond 24 hours;<sup>93,94</sup> increased mortality in childhood meningococcal septicemia has been reported in relation to etomidate use,<sup>94</sup> which is therefore not recommended in the management of sepsis and septic shock.<sup>16,90,95,96</sup> Experimental data suggest a benefit of using ketamine in sepsis because it decreases interleukin (IL)-6 and tumor necrosis factor- $\alpha$  synthesis<sup>97,98</sup> and increases endogenous norepinephrine release, helping to maintain cardiovascular stability as part of a treatment strategy to increase heart rate and SVR.<sup>99</sup> Based on these characteristics, the use of ketamine for induction is recommended unless contraindications exist.<sup>57</sup>



Continuous infusion of ketamine with benzodiazepine not only ensures proper sedation and analgesia but may also carry definite benefits in hemodynamically unstable patients.<sup>57,99</sup> To facilitate emergency endotracheal intubation and to reduce failed laryngoscopy and complication rates, properly trained and experienced practitioners may consider using short-acting muscle relaxants in addition to sedatives;<sup>2,78,100</sup> however, continuous use should be avoided, except in ARDS cases.<sup>16</sup>

### Fluid Therapy

Assessment and management of airways and respiration is followed by evaluation and optimization of the circulation. For the treatment of critically ill children, establishing vascular access as early as possible is essential;<sup>78,101–103</sup> however, it often poses a challenge. If executable quickly, peripheral venous access is acceptable, but the largest and best accessible vein should be selected.<sup>104</sup> The intraosseous route is a quick and secure alternative also in children and should be first choice in patients with shock.<sup>105–109</sup> All intravenous drugs can be used through the intraosseous route including infusions, vasoactive and inotropic drugs, and blood products.

If justified and not contraindicated, volume resuscitation must be initiated following placement of vascular access. Numerous trials have been performed with fluid therapy. In children with dengue shock syndrome, a survival rate of almost 100% was observed following fluid resuscitation, irrespective of composition of the fluid administered.<sup>110–112</sup> During the Saline versus Albumin Fluid Evaluation (SAFE) study conducted for fluid therapy of adults in the intensive care unit, no difference was found between the use of 4% albumin and normal saline in 28-day mortality, requirements of mechanical ventilation and renal replacement therapy, time at the intensive care unit and in hospital.<sup>113</sup> Given the lack of data in favor of colloid use, crystalloids should be used first line owing to their availability and better price.<sup>110–116</sup>

While previously, the primary question in fluid therapy was the choice between colloid and crystalloid solutions, today the focus has shifted to finding the ideal composition for crystalloids.<sup>117</sup> Sodium overload, hyperchloremic acidosis, and consequential renal perfusion disorder, each observed during normal saline use, all potentially worsen prognosis in critically ill patients, especially in those with associated acute kidney injury.<sup>117,118</sup> The use of so-called balanced crystalloids seems to be more advantageous,<sup>117–121</sup> a common feature of which is a cation composition more closely matching that of plasma, and a lower chloride concentration compared with normal saline. Their *in vitro* isotonicity is ensured by other anions such as lactate, gluconate, and acetate.<sup>117,120,121</sup> Owing to their potassium content and lower osmolarity, their use may be harmful in hyperkalemia, anuria, and elevated intracranial pressure.<sup>117,122,123</sup> To date, no clinical trial has confirmed superiority of the childhood use of balanced solutions. As a summary, with possible complications of sodium or chloride overload and contraindications of balanced solutions in mind, the ideal crystalloid choice must be based on an awareness

of the patient's risk factors and consideration of expected responses during the use of each solution type.

Current recommendations suggest initiation of fluid resuscitation with the administration of crystalloids (or colloid equivalent) at 20 mL/kg by push or a pressure bag,<sup>16,57,124</sup> Titrated to achieve therapeutic goals (–Table 5), 40 to 60 mL/kg and sometimes even 200 mL/kg dose might be necessary in the initial phase.<sup>16,21,57,125–127</sup> Children with persistently elevated heart rate unresponsive to fluid resuscitation should be evaluated for cardiac dysfunction. During acute stabilization and the use of large-volume fluid, no increase was detected in the incidence of ARDS and cerebral edema;<sup>57,124,128</sup> however, special attention must be devoted to signs of fluid overload during fluid resuscitation (increased work of breathing, new-onset rales, gallop rhythm, hepatomegaly), for which termination of fluid therapy and administration of inotropic agents and diuretics are recommended.<sup>16,57,129</sup>

After shock resuscitation, in cases of fluid overload exceeding 10% when native urine output fails to restore fluid balance even with the use of diuretics, peritoneal dialysis or continuous renal replacement therapy must be performed.<sup>57,130–132</sup> Fluid loss and hypovolemia due to diffuse capillary leak may persist for days; maintenance fluid requirements are largely variable, and ongoing fluid replacement must be performed under monitoring of perfusion, central venous pressure, CO, and echocardiographic control.<sup>57</sup>

### Cardiovascular Drug Therapy

Several factors need to be considered during selection and dosing of cardiovascular drugs; their delayed use significantly increases mortality.<sup>133,134</sup> Each drug may facilitate restoration of adequate organ perfusion acting on various targets, that is, by increasing contractility (inotropy) and heart rate (chronotropy), or modifying SVR (vasopressor or vasodilator effect). Pharmacokinetics and pharmacodynamics of individual drugs are influenced not only by patient age but also by organ failure (liver and kidney) developing during sepsis.<sup>57</sup> Again, it is important to note that sepsis and septic shock are dynamically changing pathologies, often necessitating modification in the dose, or replacement of medications used, or adding agents with other targets, due to changes in hemodynamic status of patients.<sup>61</sup>

Dopamine titrated to 5 to 10 µg/kg/minute is the first-choice inotropic agent in fluid-refractory shock. At doses above 10 µg/kg/minute, its α-adrenergic effect predominates, making it beneficial for use in low SVR setting.<sup>57,135</sup> Low-dose usage was previously recommended to improve renal and splanchnic blood flow and renal function; however, more recent studies and meta-analyses failed to reinforce this benefit.<sup>136–138</sup> More recent data reported about increased mortality related to dopamine administration,<sup>139–141</sup> presuming a complex underlying mechanism. Reduced gastrointestinal motility, mucosal pH, and oxygen consumption have been reported about its use,<sup>142,143</sup> in some cases potentially intensifying ventilation–perfusion mismatch,<sup>144</sup> causing multiple anomalies in the thyroid axis<sup>145,146</sup> or resulting in immune dysfunction by reducing

prolactin hormone secretion and attenuating the chemotactic effect of IL-8 on neutrophil granulocytes.<sup>145,147,148</sup>

At doses of 3 to 20 µg/kg/minute, dobutamine increases myocardial contractility and heart rate while decreasing SVR; therefore, it can be used instead of or with mid-dose dopamine in low CO associated with high or normal SVR.<sup>57,149–153</sup>

Low CO shock refractory to dopamine and/or dobutamine may be reversed with epinephrine initiated at doses of 0.02 µg/kg/minute and titrated up to 1 µg/kg/minute,<sup>61,154–157</sup> with some clinicians using it as first-line inotrope in hypodynamic shock due to the unfavorable side-effects of dopamine.<sup>57</sup> At low (<0.3 µg/kg/min) or high (>3 µg/kg/min) doses, it dominantly has β and α adrenergic effect, respectively. Ideally, epinephrine should be given through central venous access, but in emergency cases, intraosseous and peripheral venous administration is also feasible.<sup>57</sup> For a therapeutic response, it should be titrated to achieve desired effect due to its wide interpatient variability.<sup>158,159</sup> Epinephrine intensifies gluconeogenesis and glycogenolysis, with its hyperglycemic effect likely resulting in adverse outcomes. By stimulating gluconeogenesis, epinephrine enhances lactate shuttle to the liver, and plasma lactate concentration rises and becomes independent of organ perfusion, possibly impeding interpretation of the measured value.<sup>57</sup>

In the less prevalent dopamine-resistant high-CO and low-SVR setting, norepinephrine should be titrated from an initial dose of 0.02 µg/kg/minute to reach hemodynamic support endpoints.<sup>57,160</sup> In vasodilatory shock treatment, vasopressin and terlipressin, both acting independent from catecholamine receptor stimulation, might be an alternative.<sup>161–166</sup> During vasopressor use, close hemodynamic monitoring is recommended; increased SVR might lead to deterioration of myocardial contractility and consequential reduction of CO, potentially necessitating the use of inotropic agents.<sup>57,157</sup>

In normotensive patients refractory to inotropic treatment and having low CO and high SVR, nitrovasodilators can be used to reduce ventricular afterload.<sup>57</sup> Nitroprusside can be titrated for the desired effect (0.5–10 µg/kg/minute).<sup>157</sup> Type III phosphodiesterase inhibitor (milrinone, inamrinone) use may be an alternative to increase myocardial contractility and reduce SVR.<sup>167–169</sup> Their main advantage is a sustained effect even under β-adrenergic receptor down-regulation and desensitization.<sup>57</sup> Having a long half-life, they reach steady-state serum concentrations in up to several hours, driving some clinicians to give a bolus loading dose. Arrhythmia and hypotension owing to their use requires withdrawal, with the latter potentially necessitating crystalloid or colloid fluid bolus or vasopressor treatment.<sup>57,78</sup> In intractable myocardial dysfunction, levosimendan may be considered as a last resort.<sup>170–172</sup>

### Corticosteroids

In sepsis, hypothalamic–pituitary–adrenal axis affects inflammation through leukocytes, cytokines, and nitric-oxide production;<sup>173</sup> however, inflammatory cytokines might cause simultaneous insufficient adrenal output by suppression of the cortisol response to adrenocorticotropin and

may result in peripheral glucocorticoid resistance by reducing the number and affinity of receptors.<sup>174–176</sup> In sepsis, corticosteroid treatment suppresses cytokine production and increases sensitivity of the cardiovascular system to endogenous and exogenous catecholamines, thereby improving myocardial contractility, SV, SVR, and effective circulating blood volume.<sup>177</sup> Although hydrocortisone treatment might be life-saving,<sup>178–180</sup> yet data on the exact effect on mortality are still controversial.<sup>57,181–183</sup> As per current recommendations, steroid treatment should be reserved for children with catecholamine-resistant septic shock and suspected (e.g., severe septic shock with purpura, prior steroid use due to chronic illness, pituitary or adrenal abnormalities) or proven (defined as random total cortisol level less than 18 µg/dL) adrenal insufficiency.<sup>16,57</sup>

### Elimination of Pathogens

Early antibiotic therapy is crucial in the treatment of septic patients, possibly initiated within an hour.<sup>16</sup> In adults with septic shock, each hour delay from detection increased mortality by 7.6%,<sup>184</sup> whereas a retrospective study reported significantly higher mortality rates in children receiving antibiotic therapy initiated beyond 3 hours.<sup>185</sup>

Empirical antibiotic therapy should cover sensitivity of the most probable pathogens; well-selected therapy significantly reduces the risk of mortality.<sup>186</sup> Selection of the active ingredient is complex. Patient age, history (underlying illnesses, immune status, drug hypersensitivity), where primary infection was acquired (community-acquired or nosocomial), results of previous cultures (sensitivity of pathogens inducing colonization or confirmed infection), prior antibiotic treatment (last 3 months), and local antibiotic resistance should be considered during decision-making. Additionally, it is important for antibiotics to penetrate in adequate amounts into the target organ or tissue.<sup>16</sup> In sepsis treatment, bactericidal agents should be preferred over bacteriostatic ones, given that former drugs kill pathogens independent of the patient's immune system.<sup>23</sup> There are no specific guidelines on empirical antibiotic therapy; the most frequent combinations are listed in **Table 6**. If possible, consultation with a pediatric infectologist is recommended.<sup>16</sup>

Difficulties during or contraindications to culture collection (e.g., hemodynamic instability and/or coagulopathy during lumbar puncture) must not delay treatment initiation; nevertheless, successful sampling is indispensable for de-escalation of subsequent antibiotic therapy. During initial fluid resuscitation and combined antibiotic therapy, drugs given as bolus must be prioritized over infused active ingredients regarding administration sequence; concurrent use of antibiotics and fluid therapy can be facilitated through a second vascular access.<sup>16</sup>

De-escalation of empirical treatment should be done within 3 to 5 days after obtaining culture results; for subsequent infection management, the most effective monotherapy must be selected (except aminoglycoside monotherapy). Antibiotic therapy should be maintained for 7 to 10 days, but in cases of slow clinical response, immunodeficiency, source control

**Table 6** Suggested initial empiric antimicrobial regimens

Situation	Initial empiric antimicrobial regimen	Alternative regimen
Children without comorbidities (>2–3 mo)	Piperacillin (or ampicillin) + $\beta$ -lactamase inhibitor	Ampicillin + cefotaxime
		Cefotaxime or ceftazidime $\pm$ aminoglycoside
		Carbapenem
Nosocomial infection	Piperacillin + $\beta$ -lactamase inhibitor	Ceftazidime $\pm$ aminoglycoside $\pm$ glycopeptide (in case of possible MRSA or MRSE infection)
		Carbapenem
Immunosuppression, neutropenia	Piperacillin + $\beta$ -lactamase inhibitor	Ceftazidime + aminoglycoside $\pm$ glycopeptide (in case of possible MRSA or MRSE infection)
	Ceftazidime	
	Meropenem	
Suspected urosepsis or pyelonephritis	Ampicillin + aminoglycoside	Cefotaxime or ceftazidime + ampicillin (in case of possible enterococcal infection) $\pm$ aminoglycoside
Possible GI source	Cefotaxime + metronidazole	Piperacillin + $\beta$ -lactamase inhibitor
	Ampicillin + $\beta$ -lactamase inhibitor	Meropenem
Catheter-related infection	Cefuroxime	Consider adding rifampicin
	Ceftazidime or carbapenem + glycopeptide (in case of possible MRSA or MRSE infection)	
Possible MRSA infection	Add vancomycin to the empiric antibiotic regimen	Linezolid or teicoplanin
Possible MRGN infection	Meropenem	Imipenem
Severe sepsis or septic shock	Meropenem $\pm$ vancomycin $\pm$ aminoglycoside	Cefotaxime (in case of confirmed meningococcal meningitis)
Possible fungal infection	Echinocandin (micafungin or caspofungin)	Liposomal amphotericin

Abbreviations: GI, gastrointestinal; MRGN, multiresistant gram-negative bacteria; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*.

Source: Adapted from Sepsis (außer neonatale Early-onset-Sepsis). In: Berner R, Forster J, Bialek R, Borte M, DGPI - Deutsche Gesellschaft für Pädiatrische Infektiologie. DGPI Handbuch. Infektionen bei Kindern und Jugendlichen. Stuttgart: Thieme; 2013:776–784.

problems, or *Staphylococcus aureus* sepsis, longer treatment periods might be necessary. During antibiotic therapy of septic patients, hepatic and renal dysfunction, fluid compartments, and redistribution altered by fluid resuscitation may necessitate dose modification. Also, improving efficacy and minimizing toxicity risk can be promoted by measuring serum concentrations.<sup>16,23</sup>

Source control is an important component of sepsis treatment,<sup>16</sup> including debridement of various infected, necrotic tissues, drainage of infected fluids, rapid removal of objects, and foreign bodies identified as the infection source, and, through restoration of anatomic integrity and function, it aims to eliminate further contamination.<sup>187</sup> During the intervention, along with benefit from reducing the infectious inoculum, potential hazards and complications of the intervention and associated transport must be considered.<sup>188,189</sup>

### Immunoglobulins

Adjuvant treatment of sepsis with intravenous immunoglobulin (IVIG) seemed highly promising earlier; however, more recent results are controversial.<sup>190–198</sup> Most of the available

studies have small sample size and some have methodological flaws. A large randomized, controlled trial (RCT) for the treatment of sepsis in adults and a larger one in newborns found no benefit for IVIG.<sup>199,200</sup> Due to its potential toxin-neutralizing effect and an influence on facilitating opsonization of Streptococci, the use of polyclonal immunoglobulin was recommended previously in invasive group A Streptococcal infections.<sup>198,201,202</sup> Based on our current knowledge, the benefit of IVIG is doubtful in this case and its use may be considered in refractory toxic shock syndrome.<sup>16</sup>

### Red Blood Cell Transfusion and Treatment of Disseminated Intravascular Coagulation

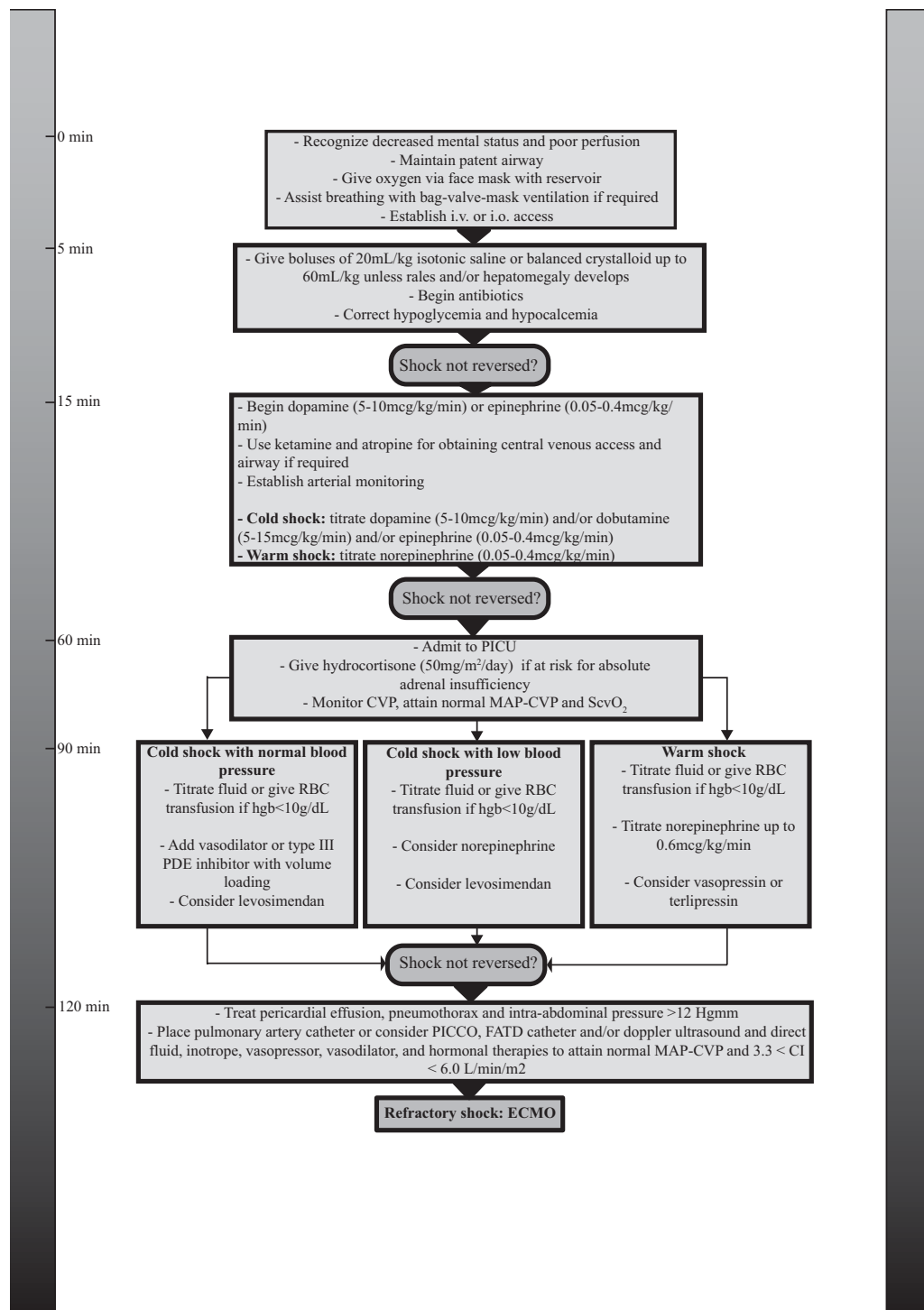
Restoration of massive cytokine release, myocardial depression, capillary leak, and abnormal tissue oxygen delivery due to acidosis, each associated with sepsis, by normalizing CO and hemoglobin levels is a cornerstone of therapy.<sup>16,57,203</sup> No optimal hemoglobin concentration is known for critically ill children.<sup>16,203,204</sup> For adults, efficacy analyses of goal-directed therapy showed better outcomes if central venous oxygen saturation could be maintained above 70% in the first 6 hours following presentation (protocol included



transfusion to attain hematocrit levels of  $\geq 30$ ).<sup>205</sup> Earlier recommendations for intensive therapy suggested higher hemoglobin goals for septic children requiring intensive care.<sup>206,207</sup> In hemodynamically stable, critically ill children, restrictive (hemoglobin threshold of 7 g/dL for red blood cell transfusion) transfusion strategy was as safe as liberal strategy (hemoglobin threshold of 9.5 g/dL for red blood cell transfusion).<sup>204,208</sup> An RCT on early goal-directed therapy of childhood septic shock confirmed better survival if 10 g/dL

was selected as transfusion cutoff.<sup>68</sup> Accordingly, hemoglobin goal is 10 g/L in hemodynamically unstable septic children during resuscitation, with this threshold being lower at 7 g/dL in stable patients.<sup>16</sup>

Disseminated intravascular coagulation is commonly observed in severe sepsis and septic shock.<sup>209</sup> Therapeutic options are controversial and lack validation.<sup>210</sup> Routine use of replacement therapy is not recommended, neither in case of mild clinical signs of bleeding,<sup>211</sup> but to stop clinically



**Fig. 1** Stepwise management of hemodynamic support in infants and children with septic shock.

significant bleeding, the use of platelet, fresh frozen plasma, and cryoprecipitate infusions might be necessary.<sup>212,213</sup>

Based on the few data available, protein C concentrate might be effective in severe sepsis associated with purpura fulminans. Improved microcirculation, moreover, lower amputation and skin graft rates were reported about its use with no adverse reactions.<sup>214–216</sup>

### Glucose Control

In septic children, disorders of glucose homeostasis are frequent. Due to peripheral insulin resistance and enhanced gluconeogenesis, there is high risk of hyperglycemia, which might be further enhanced by excessive sugar intake through infusions and total parenteral nutrition.<sup>217</sup> Neutrophil and macrophage function, as well as wound healing are deteriorated by hyperglycemia, while increasing infection and thrombosis risk.<sup>218,219</sup> Higher mortality rates and longer hospitalization were reported for hyperglycemia in critically ill children,<sup>220–222</sup> with few and controversial available data on the treatment of hyperglycemia developed during sepsis.<sup>203,223–225</sup> Until results of more recent trials become available, insulin therapy should be initiated only for blood glucose levels above 180 mg/dL, along with close blood glucose monitoring to avoid hypoglycemia, in accordance with recommendations for treatment of adults.<sup>16</sup> For note, insulin demand usually declines rapidly 18 hours from shock initiation.<sup>57</sup> Hypoglycemia can have devastating neurologic consequences and should be diagnosed early and treated immediately. Once initial hypoglycemia is resolved, children should receive 10% dextrose in normal saline ensuring a glucose intake of 2 to 8 mg/kg/minute depending on age to maintain euglycemia.<sup>16,57</sup>

### Refractory Shock

In children with refractory shock, potential associated conditions negatively influencing outcome must be revealed. Pneumothorax, pericardial effusion, and intra-abdominal hypertension may equally be mechanic causes of shock persistence, and their treatment must not be delayed after diagnosis. In adrenal insufficiency or hypothyroidism, adequate hormone substitution should be performed. In refractory shock, expansion of empirical antibiotic coverage, drainage, and debridement of the necrotic areas might be necessary. Immunosuppressive treatment should be withheld; in neutropenia, granulocyte colony-stimulating factor should be used where appropriately indicated. Excessive bleeding most frequently developed due to disseminated intravascular coagulation might indicate use of RBC and blood products.<sup>16,57</sup> If hemodynamic support endpoints cannot be reached by treating these reversible causes and in associated refractory respiratory failure, extracorporeal membrane oxygenation may be used as a last resort.<sup>226–230</sup>

### Conclusion

Therapeutic algorithm of childhood sepsis and septic shock is summarized in **Fig. 1**. Success of sepsis care is improved by properly organized emergency care and compliance with internationally accepted treatment guidelines. It is important to note that most pediatric sepsis cases can be pre-

vented; therefore, effective prevention based on screening programs, vaccination, and infection control provisions is an exceedingly important strategic move.

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