

## Recommendations for the management of pediatric septic shock in the first hour (part II)

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### ABSTRACT

In 2016, the Surviving Sepsis Campaign and the National Institute for Health and Care Excellence (NICE) developed clinical practice guidelines for the management of pediatric septic shock. In 2017, the American College of Critical Care Medicine (ACCM) updated its recommendations for hemodynamic support of pediatric shock. Recognizing septic shock is critical, as well as an optimal, time-sensitive treatment. An adequate consultation with a pediatric specialist and/or a timely referral to a facility with a higher level of care are also critical for an appropriate outcome in the management of this condition. Here we analyze the bundles used in the management of these patients, which are essential to improve the quality of care.

**Key words:** patient care bundles, septic shock, pediatrics, sepsis.

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### GLOSSARY

APP: abdominal perfusion pressure.

CVC: central venous catheter.

EI: endotracheal intubation.

HR: heart rate.

ICU: intensive care unit.

PVA: peripheral vascular access.

SBP: systolic blood pressure.

SI: shock index.

SS: septic shock.

TPP: tissue perfusion pressure.

### INTRODUCTION

Sepsis and septic shock (SS) are characterized by the inability of the cardiovascular system to meet cellular metabolic needs. An insufficient adenosine triphosphate production results in an "acute energy failure."<sup>1,2</sup> There are numerous responsible pathophysiological mechanisms, the main of which is tissue hypoperfusion.

In accordance with the SS diagnosis and treatment update, below we describe the resuscitation, stabilization, referral, and outcome measurement bundles for the management of septic shock at the emergency department before admission to the pediatric intensive care unit (ICU).

### RESUSCITATION BUNDLE

#### General aspects

Resuscitation is aimed mostly at correcting hemodynamic and metabolic alterations. This means improving oxygen delivery ( $\text{DO}_2$ ) to the tissues and reducing its demand.  $\text{DO}_2$  depends on arterial oxygen content ( $\text{CaO}_2$ ) and cardiac minute volume (CMV):  $\text{DO}_2 = \text{CaO}_2 \times \text{CMV}$ .  $\text{CaO}_2$  depends on hemoglobin and oxygen saturation ( $\text{SaO}_2$ ), while CMV depends on cardiac output and heart rate (HR). The cardiac output is determined by preload, myocardial contractility and afterload. The analysis of these variables helps to understand treatment targets.<sup>1-3</sup>

Recently, several organizations have updated their clinical practice guidelines for hemodynamic support in pediatric SS. Though recent studies conducted in adults have questioned goal-directed treatment, this is still suggested in the field of pediatrics.<sup>1,4,5</sup>

SS management starts at the recognition site (primary health care center, emergency department, hospitalization unit and/or ICU). Therefore, clinical practice guidelines for SS at the level of health care providers should be developed and published, similar to those for obstructive bronchial disease.<sup>6,7</sup> A patient seen in a pre-hospital setting, where there is no possibility for a basic

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initial treatment, should be immediately and safely transferred to a hospital once SS is diagnosed.<sup>4</sup>

### Treatment goals

These will depend on whether there is invasive monitoring available. Treatment should not be delayed due to a lack of invasive monitoring. Clinical, hemodynamic, and oxygenation goals are described below.

#### Clinical goals<sup>1,5,8</sup>

- Normalize HR for age.
- Normalize distal and central pulses.
- Normalize capillary refill.
- Normalize skin temperature.
- Normalize the sensorium.
- Optimize urine flow (> 1 mL/kg/h).

Achieving these goals using stepwise treatments has reduced pediatric SS mortality by 40 %.<sup>9</sup>

#### Hemodynamic goals

- Normalize tissue perfusion pressure (TPP)/ abdominal perfusion pressure (APP).
- Improve shock index (SI).

TPP and APP, which are overall indicators of blood flow, are priority measures at the ICU. They represent the difference between mean arterial pressure and central venous pressure or intra-abdominal pressure, respectively. The goal is to maintain normal pressure values for age (Table 1).<sup>10,11</sup>

At the emergency department, the SI [SI= HR/ systolic blood pressure (SBP)] is more practical. The goal is to reduce the SI by lowering the HR and elevating the SBP.<sup>12,13</sup>

#### Oxygenation goals

- Achieve oxygen saturation in the superior vena cava ( $\text{SaO}_{2\text{svc}}$ ) > 70 %. Oxygen saturation in the inferior vena cava ( $\text{SaO}_{2\text{ivc}}$ ) or in the right atrium ( $\text{SaO}_{2\text{ra}}$ ) is also valid.<sup>15</sup>

This is an overall tissue oxygenation indicator equivalent to mixed venous oxygen saturation ( $\text{SvO}_2$ ).<sup>16</sup> It may be measured using specimens obtained from central venous catheters (CVCs) or implantable or semi-implantable catheters. Achieving this goal reduced mortality compared to groups where SBP normalization was the only priority.<sup>17,18</sup>

### Treatment (Figure 1)

The organization of the treating team is critical and should encompass a coordinator and well-defined roles for other members, depending on available human resources. The following roles are recommended: 1) airway; 2) peripheral vascular access (PVA) and fluid administration; 3) drug preparation and infusion; 4) laboratory tests; 5) recording actions (deadlines and compliance with measures), and 6) family support and information.

Initial, basic, and universal goals include obtaining the following:

- A patent airway, with adequate oxygenation and ventilation.
- An adequate perfusion.
- Normal HR for age.

Actions should include the following:

- Recognize altered sensorium and perfusion.
- Maintain a patent airway and assess the need for endotracheal intubation (EI).
- Administer  $\text{O}_2$  (either through a mask, high-flow nasal cannula or mechanical ventilation).
- Establish at least 2 PVAs (or prepare implantable or semi-implantable catheters or intraosseous access).
- Begin non-invasive hemodynamic monitoring: serial measurement of blood pressure, pulse oximetry, continuous electrocardiogram, temperature, urine flow.
- Measure blood glucose and calcium.

TABLE 1. Heart rate and tissue perfusion/abdominal pressure thresholds for age

	Heart rate (beats per minute) <sup>a</sup>	Tissue perfusion <sup>b</sup> /abdominal pressure
Neonates (< 30 days)	110-160	MAP [55 + (age x 1.5)] – CVP or IAP = 55
Infants (1 to 23 months old)	90-160	MAP [55 + (age x 1.5)] – CVP or IAP = 58
Children (2 to 7 years old)	70-150	MAP [55 + (age x 1.5)] – CVP or IAP = 65

MAP: mean arterial pressure; CVP: central venous pressure; IAP: intra-abdominal pressure.

<sup>a</sup> Acceptable thresholds for heart rate are defined by the Pediatric Risk of Mortality (PRISM) score.

<sup>b</sup> The target tissue perfusion pressure is based on the formula estimated for the 50<sup>th</sup> percentile of MAP for a healthy child with the 50<sup>th</sup> percentile for height and a CVP of 0 mmHg.

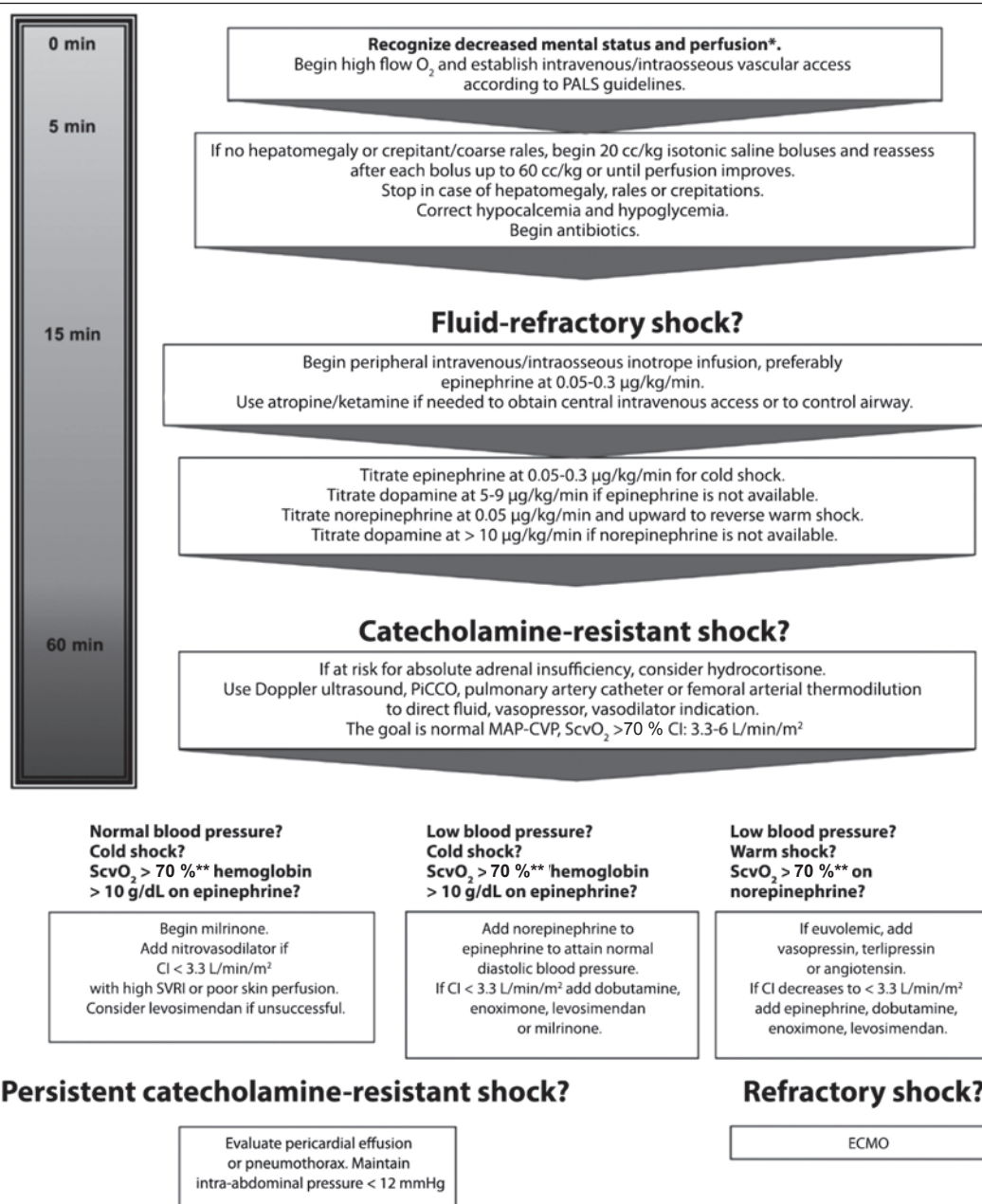
When CVP is > 0, the target MAP should be adapted to the target of an adequate perfusion pressure.

Adapted from the American College of Critical Care Medicine.

Once airway patency is warranted, and spontaneous breathing and circulation are confirmed, supplementary O<sub>2</sub> should be given using a mask with reservoir bag or a high-flow nasal cannula to prevent both hypoxia and hyperoxia (SaO<sub>2</sub> 100 %).<sup>1,19</sup>

EI should be done if breathing work increases, cardiopulmonary insufficiency progresses (with bradycardia, bradypnea and hypotension) or the Glasgow score is < 8. If possible, an adequate fluid preload and/or inotrope administration should be warranted in advance due to the frequent

FIGURE 1. Septic shock management algorithm. Adapted from the 2017 Consensus by the American College of Critical Care Medicine<sup>1</sup>



\* It is suggested that each facility should have a diagnostic algorithm, perform a clinical control within 15 min in each patient with a positive screening, and start resuscitation in the first 15 min.

\*\* Except patients with congenital heart disease and mixed lesions.

PALS: Pediatric Advanced Life Support; O<sub>2</sub>: oxygen; MAP: mean arterial pressure; CVP: central venous pressure;

ScvO<sub>2</sub>: central venous oxygen saturation; CI: cardiac index; ECMO: extracorporeal membrane oxygenation;

PiCCO: pulse induced contour cardiac output; SVRI: systemic vascular resistance index.

presence of relative/absolute hypovolemia and/or myocardial dysfunction. Likewise, drugs used to facilitate EI may aggravate the hemodynamic problem.<sup>1</sup>

The preliminary results of a study conducted by the Latin American Society of Pediatric Emergency Medicine (*Sociedad Latinoamericana de Emergencia Pediátrica*, SLEPE) showed that 47 % of emergency physicians decided to perform an EI in children with SS, even in the absence of respiratory insufficiency.<sup>20</sup>

PVAs are suggested to achieve the initial goals. If not possible after 5 minutes, an intraosseous access should be obtained –which is safe, easily placed, allows to administer drugs and fluids and collect lab specimens.<sup>21</sup> An ultrasound may facilitate the placement of a CVC, but requires trained skills, equipment, and time.<sup>22,23</sup>

Lab specimens (blood calcium, blood glucose, blood count, liver and kidney function, lactic acid, coagulation profile, ionogram, and acid-base status) should be collected to correct alterations and identify multisystem involvement.<sup>1,4</sup> The collection of specimens for cultures is recommended, but this should not delay antibiotic therapy.<sup>1,4</sup>

Non-invasive monitoring includes measuring respiratory rate, HR, blood pressure, SI, SaO<sub>2</sub>, urine flow, rectal and/or axillary temperature. These measurements should be often recorded in a sheet.

Then, the following should be done:

- Begin crystalloid boluses at 20 mL/kg up to 40-60 mL/kg in 30 minutes. Control for volume overload signs after each bolus (hepatomegaly, rales, cough, and a third heart sound).
- Correct hypocalcemia and hypoglycemia.
- Give antibiotics.
- Begin and titrate vasoactive drugs via PVA or intraosseous access (if CVC is not available).

Fluid “bolus” resuscitation using 20-mL or 60-mL syringes is started immediately after obtaining a vascular access. This technique is preferred over a “continuous drip” and/or infusion pump, which not always reach the necessary volume over an adequate time. After each bolus, the patient should be controlled for signs of volume overload, as mentioned above.

If shock signs are reversed or overload signs develop, fluid administration should be discontinued. In case of the latter or if 40-60 mL/kg are being administered without improvement, begin vasoactive drug infusion via a PVA or intraosseous access, if no CVC is available.

Volume resuscitation requirements may be 0 mL/kg if rales or hepatomegaly develop, although, in general, they are set at 40-60 mL/kg initially.<sup>24</sup>

Infused volumes and administration duration should be controlled and recorded in a strict manner.

Crystalloid solutions are the first choice due to their low cost and high availability, although they show a greater incidence of electrolyte disorders and acute kidney injury and require higher volumes than colloid solutions.<sup>25-27</sup>

Balanced solutions (crystalloid solutions with a lower chlorine concentration) are an option but there are no studies indicating their superiority over traditional crystalloids.<sup>28-30</sup>

Colloids rapidly expand the intravascular space and stay there longer, but they are expensive, cause clotting alterations, and reduce ionic calcium with a negative inotropic effect, and there is no evidence indicating their superiority over crystalloids.

Children with complicated heart disease, prior heart failure or risk for cardiomyopathy (malnourished, history of myocarditis, cancer patients who are receiving or received anthracyclines) should begin fluids at 5-10 mL/kg over not less than 20 minutes, with frequent monitoring for overload signs.<sup>1,3</sup>

Peripheral edemas, typical of SS capillary lesions, are not always a synonym of hypervolemia or a contraindication to fluid administration.<sup>2</sup>

Although some authors propose a restricted fluid administration strategy, especially in facilities with a lower level of care,<sup>31</sup> an “adequate” initial strategy and patient monitoring after each bolus are suggested.<sup>1,4,32,33</sup>

Clinical practice guidelines recommend reaching fluid administration goals in the first 15 minutes, which, in practice, is hardly achievable. The SLEPE conducted a survey that showed that 56 % of respondents achieved fluid administration goals over 30-60 minutes, and 37 %, in less than 30 minutes.<sup>20</sup> Sankar et al., observed that bolus administration in less than 10 minutes showed greater risks for EI than administration over 15-20 minutes.<sup>34</sup> A limit of 30 minutes is suggested as a more reasonable goal.

Antibiotic administration in the first hour improves the clinical course and reduces mortality due to SS.<sup>35-39</sup> Initial empiric antibiotic regimes should consider the source of infection and be adequate by 48 or 72 hours of receiving the corresponding culture results. Antibiotic choice



should be based on the most likely presumed infectious agent, the type of host, his/her age, nosocomial or community acquisition, and institutional epidemiology; the one with the lower toxicity and cost should be chosen.

Metabolic alterations may worsen the condition. A lack of intracellular glucose worsens energy failure. An anion gap  $> 16$  mEq/L suggests glycopenia. To prevent glycopenia and improve glucose intake, 10 % dextrose solutions at 4-6 mg/kg/min are recommended, so as to maintain blood glucose levels between 80 and 150 mg/dL.<sup>1,5</sup> Hyperglycemia is also harmful. Blood glucose levels  $> 178$  mg/dL double the risk for death in children with SS.<sup>40</sup> In case of blood glucose  $> 150$  mg/dL, insulin administration should be started.<sup>1</sup>

Hypocalcemia should be corrected as per usual practice due to the effects of calcium on inotropism.<sup>1</sup>

Bicarbonate should not be given to patients with SS and pH  $> 7.15$  because it is associated with sodium overload, volume overload, increase in serum lactate and partial pressure of carbon dioxide, and ionic calcium reduction.<sup>41,42</sup>

Vasoactive drugs are indicated subsequently. The impossibility to place a CVC, mostly due to the user's inexperience, is a barrier for the early administration of drugs.<sup>43</sup> Infusion via a PVA has been validated by the authors of this and other studies. Side effects are scarce and, if any, they develop 6 hours after infusion.<sup>1</sup> Side effects may be prevented by diluting vasoactive drugs 10 times more than when administered via a CVC.<sup>1,44-51</sup>

Adrenaline is indicated for cold shock (0.05 µg/kg/min up to 0.3 µg/kg/min) in an attempt to optimize cardiac contractility due to its beta-agonist effect at these dose ranges. For warm shock, alpha agonists (0.1 µg/kg/min and higher doses) are recommended. Dopamine is associated with a higher mortality compared to adrenaline and noradrenaline, and is reserved as a second-line choice.<sup>52-56</sup> Other vasoactive drugs may be used looking for specific hemodynamic effects: inotropes, such as milrinone, to improve contractility, or vasopressors, like vasopressin, in case of vasodilation uncontrolled with noradrenaline (*Tables 2 and 3*).

## STABILIZATION BUNDLE (GENERALLY AFTER 60 MINUTES)

A lack of response to the initial resuscitation measures requires invasive monitoring and ICU-

relevant management that exceed the objectives of this study. Until a patient is transferred to the ICU, a goal-directed treatment should be followed.

Objectives include the following:<sup>1</sup>

- Normal perfusion, normal HR for age.
- Adequate TPP / APP for age.
- ScvO<sub>2</sub>  $> 70$  %.
- Optimized mechanical ventilation.

Actions should include the following:

- Complement initial monitoring with basic invasive monitoring (continuous intra-arterial blood pressure, central venous pressure, and ScvO<sub>2</sub>).
- Monitor for the development of compartmental syndrome and pneumothorax, and treat them.
- Titrate glucose, calcium, lactate, anion gap, and hematocrit levels and coagulation profile.
- Adjust the administration of fluids, vasoactive drugs, and hormones based on multimodal monitoring.
- Control the source of infection (collection drainage, etc.).

## REFERRAL BUNDLE

Teams specialized in critical care and rapid response, which have been recently developed, have reduced mortality and improved the clinical course of SS.<sup>57,58</sup> If sepsis is suspected in a child, trained staff, such as pediatric emergency physicians, pediatric intensivists or pediatric hospitalists, should be consulted about an adequate and timely treatment. If the patient does not respond in the first hour after initial resuscitation, he/she should be seen by a specialist.<sup>4</sup>

Telemedicine (remote consultation using IT devices, such as mobile phones, computers, etc.) allows an expert to "virtually and distally see" a patient who is at a facility with a lower level of care. It is relatively simple, more accurate than a telephone consultation, more comfortable for the health care provider at facilities with a lower level of care, and improves processes and reduces costs.<sup>59-62</sup> In the province of San Luis, Argentina, positive results were reported using this modality.<sup>63</sup>

## OUTCOME MEASUREMENT BUNDLE

Different studies have reported care process improvements after the implementation of this bundle.<sup>1,5,64-67</sup>

In New York, USA, hospitals are required to develop sepsis protocols focused on early

recognition and treatment, implement them, and report results to the government and the community.<sup>68</sup>

The following measurements are recommended:

- Bundle adherence.
- Achievement of goals.
- Barrier description.

- Observed unwanted effects.
- Adherence to antibiotic administration in the first hour.

## OTHER THERAPEUTIC CONSIDERATIONS

### Hormonal therapy

These children may require hormonal therapy, although there is no agreement in this regard.<sup>1,69-72</sup>

TABLE 2. Vasoactive drugs used in cold septic shock in the first hours in children<sup>1,77,78</sup>

Cold shock				
Drug	Dose	Receptor	Effect	Remarks
<b>Adrenaline</b>	<b>Initial:</b> 0.05-0.3 µg/kg/min <b>Treatment:</b> Titrate for inotrope doses Up to 0.3 µg/kg/min For inoconstrictor doses 0.4-0.8 µg/kg/min <b>Objective:</b> Stimulate β <sub>1</sub> and β <sub>2</sub> receptors	α <sub>1</sub> , α <sub>2</sub> , β <sub>1</sub> , β <sub>2</sub>	↑ Inotropism (β <sub>1</sub> ) ↑ Chronotropism (β <sub>2</sub> ) Arterial and venous vasoconstriction (α <sub>1</sub> ) Arterial vasodilatation β <sub>2</sub>	Dilute 10 times for peripheral or intraosseous access or indicate other parallel infusion for dilution. Dose: > 0.3 µg/kg/min: Risk for renal ischemia, myocardial ischemia, and pulmonary hypertension.
<b>Dopamine</b>	<b>Initial:</b> 5-9 µg/kg/min <b>Treatment:</b> Titrate for inotrope doses Up to 15 µg/kg/min Titrate for vasopressor doses > 15 µg/kg/min	α <sub>1</sub> , α <sub>2</sub> , β <sub>1</sub> , DA <sub>1</sub>	↑ Inotropism (β <sub>1</sub> ) ↑ Chronotropism (β <sub>2</sub> ) Arterial and venous vasoconstriction (α <sub>1</sub> )	Greater mortality than with adrenaline and/or noradrenaline.
<b>Dobutamine</b>	<b>Initial:</b> 10 µg/kg/min <b>Treatment:</b> Titrate for inotrope doses Up to 20 µg/kg/min	β <sub>1</sub> , β <sub>2</sub>	↑ Inotropism (β <sub>1</sub> ) ↑ Chronotropism Minimum effect β <sub>2</sub>	
<b>Milrinone</b>	<b>Initial:</b> Assess load at 50 µg/kg in 15 min <b>Treatment:</b> Titrate for inotrope doses 0.25-0.75 µg/kg/min	Phosphodiesterase inhibitor Increases cyclic adenosine monophosphate	↑ Inotropism Arterial vasodilation	Acts in a synergistic manner with β-adrenergic receptors.
<b>Inamrinone</b> (formerly amrinone)	<b>Treatment:</b> Titrate for inotrope doses at 5-10 µg/kg/min	Phosphodiesterase inhibitor Increases cyclic adenosine monophosphate	↑ Inotropism Arterial vasodilation	Acts in a synergistic manner with β-adrenergic receptors.
<b>Levosimendan</b>	<b>Treatment:</b> Current trend Single dose via continuous perfusion over 24 h at 0.2 µg/kg/min (total maximum dose of 12.5 mg)	Increases Ca <sup>++</sup> /actin/tropomyosin binding Lower phosphodiesterase inhibitory activity	↑ Inotropism	
<b>Nitroglycerin</b>	<b>Treatment:</b> 0.5-10 µg/kg/min		Venous vasodilation	
<b>Nitroprusside</b>	<b>Treatment:</b> 0.2-6 µg/kg/min		Arterial and venous vasodilation	Toxicity caused by thiocyanate

µg/kg/min: microgram/kilogram/minute; mg: milligram; α<sub>1</sub>, α<sub>2</sub>: alpha 1 and alpha 2; β<sub>1</sub> and β<sub>2</sub>: beta 1 and beta 2; Ca<sup>++</sup>: ionic calcium; DA<sub>1</sub>: dopamine receptor antagonist.

Hydrocortisone is suggested only in children with catecholamine-refractory septic shock and/or suspected or proven adrenal insufficiency. Patients receiving prolonged corticosteroid treatment, with central nervous system diseases and/or alterations in adrenocorticotrophic hormone (ACTH) production or purpura fulminans who do not respond to vasoactive drugs are at a higher risk for adrenal insufficiency. In adults, low doses are effective (hydrocortisone 100 mg/m<sup>2</sup>/day in 4 doses). In children, an initial dose of 2 mg/kg, followed by 1 mg/kg every 8 hours, is recommended.<sup>73,74</sup>

Hypothyroidism may appear as a clinical presentation after the administration of corticosteroids and should be recognized and treated promptly.<sup>1</sup>

### Blood and blood products

Although some previous recommendations established to set a target hemoglobin value higher than 10 g/dL, the current evidence suggests conservative targets for blood transfusion in critically-ill children without cardiopulmonary involvement and reserves its indication if hemoglobin is lower than 7 g/dL.<sup>75,76</sup> Children with SS and severe anemia (hemoglobin < 6 g/dL) require more transfusions than fluids. Moreover, fluids may worsen anemic shock.<sup>31</sup>

Children with clinical signs of disseminated intravascular coagulation or purpura fulminans and active bleeding should receive fresh frozen plasma and blood products.<sup>1,4</sup>

In pediatrics, there are no recommendations for platelet transfusion in children with SS. It is suggested to transfuse less than 5000 platelets/dL if there is bleeding or risk for any procedure.

### CONCLUSIONS

SS management requires a series of measures, starting with recognition, which triggers the timely administration of time-sensitive treatments.

Limitations in some areas where the initial measures are taken require a consultation with a specialist and/or an optimal referral to a facility with a higher level of care.

It is very important to assess these processes in order to improve the quality of care for children with sepsis; and the health care team, facilities in particular and governments in general should all become involved. ■

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TABLE 3. Vasoactive drugs used in warm septic shock in children<sup>1,77,78</sup>

Warm shock				
Drug	Dose	Receptor	Effect	Remarks
Noradrenaline	<b>Initial:</b> 0.05 µg/kg/min <b>Treatment:</b> Titrate for vasopressor doses <b>Target:</b> stimulate α <sub>1</sub> receptors	α <sub>1</sub>  Mild effect on β <sub>1</sub> No effect on α <sub>2</sub>	Vasoconstriction ↑ Mild inotropism ↑ Mild chronotropism	Dilute 10 times for peripheral or intraosseous access or use other parallel infusion for dilution. Sensibility does not depend on age.
Dopamine	<b>Initial:</b> > 10 µg/kg/min <b>Treatment:</b> Titrate for vasopressor doses > 15 µg/kg/min	α <sub>1</sub> , α <sub>2</sub> , β <sub>1</sub>	↑ Inotropism (β <sub>1</sub> ) ↑ Chronotropism (β <sub>2</sub> ) Arterial and venous vasoconstriction (α <sub>1</sub> )	Greater mortality than with adrenaline and/or noradrenaline.
Vasopressin	<b>Treatment:</b> Titrate for vasopressor doses 0.0003-0.008 U/kg/min	v <sub>1a</sub> , v <sub>1b</sub> and v <sub>2</sub>	Arterial vasoconstriction	

µg/kg/min: microgram/kilogram/minute; U/kg/min: unit/kilogram/minute; α<sub>1</sub>, α<sub>2</sub>: alpha 1 and alpha 2; β<sub>1</sub> and β<sub>2</sub>: beta 1 and beta 2; v<sub>1a</sub>, v<sub>1b</sub> and v<sub>2</sub>: vasopressin receptors 1a, 1b, and 2.

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