

# Practical guidelines in the treatment of septic shock in children

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## ABSTRACT

The article focuses on the clinical recognition of septic shock, the basic investigations and the hierarchical treatment based on recent international therapeutic protocols, being especially useful in services that do not have pediatric intensive care units.

**Keywords:** septic shock, diagnosis, emergency treatment

This material is based on the chapter “Shock” contained in the Treatise on Pediatrics\* published in 2021 and was redacted because in the interval between the writing of the manuscript, the publication of the book and the current moment, new data has been accumulated whose updating the author considered necessary

Septic shock is an evolution of sepsis in which deep circulatory, cellular and metabolic disorders generate a high risk of mortality [1]. Sepsis and septic shock are a major cause of morbidity and mortality in the pediatric population, often very difficult to diagnose and treat [2]. Identifying sepsis and providing a correct treatment in the first hour after presentation can be decisive for saving the patient’s life. The first hour of treatment is well codified in numerous guidelines and therapeutic algorithms, it being known that every hour the child remains in septic shock doubles the risk of death [3]. Most of the principles of diagnosis and treatment in septic shock in children were influenced by International Treatment Guidelines for adults [4-6]. Recently, an extensive material signed by 51 prestigious authors dedicated to evidence-based recommendations in

the treatment of septic shock in children generated a rational basis for approaching their therapeutic plan [7]. The article gives a significant space to the therapeutic conduct from the first hour, with the mention that in the case of locations with limited resources, this must be adapted to the local conditions, the experience and the competence of the medical team, as confirmed by the study of a team from India [8].

## Clinical

The onset of the syndrome is non-specific. The first observation may come from parents who find that “the child does not look good”. Refusal of food, fever, tachypnea, tachycardia, drowsiness, marbling of the skin are soon added to these. Specific organ manifestations such as cough, diarrhea, vomiting, convulsions quickly appear. *It is important that the first significant clinical changes are noticed by the doctor, and directing the child to a specialized service in time can make the difference between life and death.* With the progression and generalization of the infection, respiratory distress, abdominal distention, oliguria, decreased reactivity, cold marbled

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extremities, prolongation of capillary recoloration time, petechiae, jaundice may appear.

**Alarm signs**

Alarm signs at the clinical examination: fever >38° C under 3 months, >38.5° C over 3 months, hypothermia <36° C under 3 months, persistent tachycardia, tachypnea, weak pulse, prolongation of capillary recoloring time, hypotension, changes in mental state irritability, drowsiness, lethargy, confusion), purpura (meningococcal meningitis?), macular erythema (toxic shock syndrome?).

**Signs/symptoms of infection:** fever, toxic appearance, signs of dehydration, hypotension, convulsions, nuchal rigidity, respiratory failure, rales, abdominal bloating, cellulitis, lymphangitis, abscesses, adenopathies. The initial clinical orientation is determined by some vital signs and the first laboratory changes

Differential diagnosis

- In newborns and infants: hereditary metabolic diseases, ulceronecrotic enterocolitis;
- Severe localized infections: pneumonia, osteomyelitis, meningitis, peritonitis;

- Viral infections with systemic effects: herpes infection, CM infection;
- Leptospirosis;
- Diabetic coma, other decompensated metabolic diseases;
- Drug poisoning, sunstroke;
- Massive pulmonary embolism;
- Other types of shock: hypovolemic shock, cardiogenic shock, hemorrhagic shock, toxic shock syndrome, anaphylactic shock, Stevens-Johnson syndrome (toxic epidermal necrosis).

**TREATMENT**

Requires the existence of a trained and competent team capable of reacting regardless of the patient’s presentation time. In hospital services without pediatric intensive care units, the patient is taken over by the attending physician or the on-call physician. The doctor on duty must always be requested, whose presence is strictly necessary. The clinical condition and the evolution under treatment must be noted in the patient’s observation sheet at as short intervals as possible (Attention, the

**TABLE 1.** Cardiorespiratory vital signs and some significant changes in infectious shock in children. According to Emr et al [8], modified; Weiss et al\* [7]

Age group	Tachycardia (beats/min)	Bradycardia (beats/min)	Tachypnea (resp/min)	Systolic BP (mmHg) Hypo BP	Leucocyte count (leuc x 10 <sup>3</sup> /mm <sup>3</sup> )
0 days - 1 week	>180	<100	>60	<65	>34
1 week - 1 month	>180	<100	>50	<75	>19.5 or <5
1 month - 1 year	>150	<90	>50	<50*	>17.5 or <5
2-5 years	>140	<60 sau <80	>22	<60*	>15.5 or <6
6-12 years	>120	<60 sau <70	>20	<70*	>13.5 or <4.5
13-18 years	>110	<60	>14	<90	>12 or <4.5

**TABLE 2.** The first urgent investigations at the patient’s presentation

<b>Metabolic</b>	Blood glucose, lactic acid, urea, creatinine, ionogram, Ca, transaminases, blood gases*
<b>Hematological</b>	HLG, prothrombine time, fibrinogen
<b>Etiological</b>	Blood culture, urine culture, CSF (if suspected)
<b>Depending on the clinical condition</b>	Rgr: chest, abdomen, echocardiography (if suspected)

\*Modern automatic blood gas and electrolyte analyzers determine, along with lactic acid, blood sugar, as well as other parameters

**TABLE 3.** Significant investigations in children in a state of septic shock/systemic inflammatory response. Modified after Weiss and Pomerantz, 2018 [13]

Leukocytosis (over 15,000/mm <sup>3</sup> ), the presence of immature forms, vacuolated neutrophils, toxic granules, leukopenia (below 4000/mm <sup>3</sup> )
Platelets below 80,000/mm <sup>3</sup>
Evidence of disseminated intravascular coagulation (DIC): increase in D-dimers, INR, PT/PTT
Lactic acidosis (serum lactate >2 mmol/l)
C-reactive protein (values above 100 mg/dl, significant)
Procalcitonin > 10 ng/ml (significant for sepsis)
Renal failure (creatinine > 2 times the normal limit for age)
Liver dysfunction: total bilirubin > 4 mg/dl (not in newborns), ALT >2 times the normal limit for age
<b>Blood culture (impossibility of collection do not delay administration of antibiotics)</b>

FO can constitute a medico-legal document at any time]. At the same time, the team of doctors and nurses must be mobilized, each having very clear tasks. Fast venous access is essential, preferably for 2 veins; in case of failure, intraosseous access is used. In a 60' interval, a series of objectives must be sequentially covered in a resuscitation “bundle” [9-11]

**TABLE 4.** Approach to septic shock: objectives for the first 60'

- Airway permeability and O<sub>2</sub> supply
- IV or IO vascular access in the first 5'
- Blood collection for blood culture
- Determination of serum lactate, acid-base parameters, blood sugar (offered by the automatic analyzer if available)
- Administration of 0.9% saline solution or balanced solutions IV from the first minutes
- Antibiotics from the first 60'
- Vasoactive agents in shock refractory to volume repletion after 60'

**Sustaining the flow of O<sub>2</sub>** is initiated after checking the patency of the airways. At the source, the O<sub>2</sub> concentration (FiO<sub>2</sub>) is 100%. The degree of oxygenation is monitored by continuous pulse oximetry (SpO<sub>2</sub>) to avoid increasing SpO<sub>2</sub> over 97% with adverse effects on the lungs, microcirculation (vasoconstriction), the production of hyperoxia and oxygenated free radicals. O<sub>2</sub> administration can be done through nasal cannula 2-4 l/min or through cephalic tent 7-15 l/min to maintain SpO<sub>2</sub> between 88-92%. In case of respiratory, circulatory or neurological impairment, endotracheal intubation and mechanical ventilation are used. Endotracheal intubation and sedation reduce the work of breathing and divert cardiac output to the respiratory muscles [12].

#### Fluid resuscitation

Any patient in septic shock can be considered hypovolemic and volemic repletion is an essential component of the treatment. Liquid therapy begins with the administration of 0.9% saline solution, or preferably Lactat Ringer's solution or Plasma-Lyte 10-20 ml/kg administered by syringe from the first 5 minutes following the appearance of signs of hemodynamic improvement. The International Guideline for the Treatment of Septic Shock in Children, 2020 [7] recommends the use of balanced crystalloid solutions compared to 0.9% saline solution, which could be correlated with hyperchloremic acidosis, systemic inflammation, coagulopathy, in studies conducted on adults who received large amounts of fluids. The authors consider that liquid repletion with 0.9% saline can be preferred in patients with hyponatremia and in those with increased intracranial pressure. Most frequently, it is necessary to re-

peat at least 3 boluses of 20 ml/kg administered quickly in the first 60'. After each administration, it is important to assess the clinical condition and hydration status. The improvement is evident by the normalization of the heart rate, the respiratory rate, the improvement of the state of consciousness, the increase of the urinary flow and the return of the capillary recoloring time below 2" [7,14].

**TABLE 5.** Fluid overload: clinical recognition criteria

- Tachypnea
  - Basal rales
  - Hepatomegaly
- The same clinical signs can direct the diagnosis to a cardiac dysfunction due to cardiogenic shock

**TABLE 6.** Therapeutic plan in septic shock in specific conditions. According to Weiss et al. [7]

- In children with septic shock without signs of fluid overload, **without arterial hypotension**, in locations with limited resources where advanced support and intensive therapy are not available, it is not recommended to administer fluids in bolus, but to start with maintenance fluids in the first hour for treatment.
- **If hypotension is present**, administer liquids up to 40 ml/kg in boluses of 10-20 ml/kg in the first hour, followed by additional 10 ml/kg in the next 30' if there are no signs of improvement. Children with gastroenteritis are excluded from this rehydration scheme, digestive losses being replaced by specific therapy.

In malnourished and anemic children, excessive volemic resuscitation in the first hours of treatment can produce fluid overload, subsequently requiring fluid restriction and the use of diuretics (de-resuscitation) [7,13,15]. During the first hour of treatment, it must be established whether the patient responds to volemic repletion. If there are no signs of improvement, or if the condition worsens, it is necessary to introduce inotropic therapy. In this important period for survival, antibiotic treatment and correction of any hypoglycemia or hypocalcemia must be initiated.

#### Monitoring

All children in a state of septic shock must be continuously overseen by monitoring heart rate, breathing, pulse oximetry and frequent blood pressure measurement [13]. In the services where there are possibilities, the determination of mean arterial pressure (MAP) provides indications on the rate of recovery of volume. Under usual conditions, the determination of systolic BP is a reasonable alternative [7]. As indicators of severity, metabolic acidosis with base deficit >5.0 mEq/l and an increase in serum lactate above >1 mmol/l or >2 (18mg/dl) are added (reflects tissue hypoperfusion, cellular anaer-

obic metabolism and energy depletion) [18]. Lactate equal to or above 4 mmol/l upon admission to the PICU is a predictor of unfavorable evolution [19]. The authors [7] recommend not to use the terms “warm shock” and “cold shock” because they do not correlate with the cardiac index and peripheral vascular resistance.

### Changes in blood sugar

Hypoglycemia occurs frequently in newborns (<45 mg/dl) and infants/children (<60 mg/dl) in septic shock. Its correction must be done quickly with IV glucose 2-4 ml/kg of the 25% solution (maximum concentration for administration on the peripheral vein), or 10% glucose 5-10 ml/kg IV, 2-4ml/kg in newborns [13]. After the administration of a glucose bolus, the infusion of a 5-10% glucose solution must

maintain blood glucose within normal limits or within safety limits (70-150 mg/dl) if oral nutrition is not possible [25]. Hyperglycemia over 180 mg/dl is a marker of severity, but the option to maintain blood sugar below 140 mg/dl by administering insulin is a risk factor [7]. Even short periods of severe hypoglycemia can cause long-term sequelae.

### Hypocalcemia

Defined by the decrease of serum Ca below 8.5 mg/dl and ionized Ca below 4.2 mg/dl can be asymptomatic or add some specific manifestations to the shock: apnea, cyanosis, tremors, convulsions, abdominal distension, cardiac arrhythmia and prolongation of the QT interval on the ECG trace. The administration of calcium gluconate sol 10% in a dose of 0.5-1 ml/kg is done slowly IV or IO (**ie over 5'**) and

**TABLE 7.** The empirical choice of antibiotics in the treatment of septic shock or in case of etiological suspicion. According to Weiss, Pomeranz 2018, modified [13]. It should be mentioned that the choice of antibiotics can be modified depending on the particularities of the pathology and the availability of the service.

0-28 days	Ampicillin to be replaced with vancomycin 15 mg/kg initial dose in suspected St aureus MRSA infection + cefotaxime 50 mg/kg initial dose + gentamicin 2.5 mg/kg initial dose + aciclovir 20 mg/kg/dose for suspected herpes virus infection
Children	Vancomycin 15 mg/kg as initial dose (max 1 g/dose) IV every 8 hours (total dose 45 mg/kg/day) + Ceftriaxone 75 mg/kg (max 2 g as initial dose) single intake/24 hours OR Cefotaxime 100 mg/kg (max 2 g as initial dose), 100 mg/kg/24 for newborns/infants; >12 years 1(2)g every 12 hours
Children > 28 days in immunosuppression or at risk of infection with Pseudomonas aeruginosa	Vancomycin 15 mg/kg (max 1-2 g as initial dose) + cefipime 50 mg/kg (max 2 g initial dose) OR carbapenems (imipenem, meropenem) in extended bacterial resistance or in patients treated in the last 2 weeks with cephalosprine generation III or fluoroquinolones
Children who have recently received broad-spectrum antibiotics (or cannot receive penicillin)	Vancomycin in age-appropriate doses + meropenem (<3 months 20 mg/kg initial dose; > 3 months 20 mg/kg, max 2 g initial dose) Instead of meropenem + Aztreonam or ciprofloxacin + clindamycin
Children at risk of fungal infections	Immunocompromise with persistent fever under broad-spectrum antibiotics or identified fungal source To add amphotericin B to the antibiotic treatment

**TABLE 8.** Inotropic/vasopressor medication in septic shock in children. According to Davis et al. [24], Weiss and Pomeranz, [25] modified

Vasoactive agent	Doses, effects
Epinephrine (adrenaline)	Sol 1% 1ml = 1mg 0.05-0.3 mcg/kg/min, inotropic effect (increases TAs, AV) 0.3-1(2) mcg/kg/min, vasoconstriction, increases BP * Most authors prefer epinephrine as initial therapy over dopamine; at high doses, careful cardiac and BP monitoring
Dopamine	5-10 mcg/kg/min, inotropic dose 10-20 mcg/kg/min, vasopressor dose in hypotensive patients with normal circulating volume * It is a time-tested inotrope, it can be administered safely via the peripheral vein
Norepinephrine	0.03-0.05 as a starting dose, or 0.05-0.1 [1] mcg/kg/min in prolonged hypoTA after repletion. Produces vasoconstriction, increases cardiac and AV contractility
Dobutamine	2-20 mcg/kg/min increases cardiac output in case of low cardiac performance with normal or increased peripheral vascular resistance

if possible on a large vein or on a central line [25,27]. Paravenous administration of Ca can cause severe skin necrosis.

### Treatment of the infection

The administration of antibiotics must be initiated within the first hour after approaching the pa-

tient, even if it is not possible to collect a blood culture within this interval.

### Vasoactive therapy

Ideally, after the first hour of treatment, the doctor must determine whether the patient responds to the administration of fluids or not [13]. The decision

**TABLE 9.** How to prepare inotropic/vasopressor solutions using the “rule of 6” According to Schexnayder [16], Craiu [17]

Medication	Preparation of the solution	Infusion rate
Dopamine Dobutamine	Weight in kg x 6 = the amount of medicine (mg) to be added to 100 ml of infusion liquid	1ml/hour = 1mcg/min (eg to deliver 10 mcg/kg/min the infusion is adjusted to 10 ml/hour)
adrenaline (epinephrine) Norepinephrine	Weight in kg x 0.6 = the amount of medicine (mg) to be added to 100 ml of liquid to be infused	1ml/hour = 0.1 mcg/kg/min (ex to deliver 0.3 mcg/kg/min the infusion is adjusted to 3 ml /hour)

Conversion of mg to mcg: 1 mg= 1000 mcg (ug)

**TABLE 10.** Therapeutic algorithm in septic shock in children. Adapted from the Australian Commission on Safety and Quality in Health Care. Sepsis Clinical Care Standard, Sydney: ACSQHC;2022 [22]

Time targets	<p><b>Sepsis/ septic shock recognition</b>  <b>Sepsis should be considered in a patient with suspected or proven infection AND/OR fever/hypothermia (Temp <math>\geq 38^\circ</math> or <math>&lt;36^\circ</math>) AND one or more signs of impaired tissue perfusion below:</b></p> <ul style="list-style-type: none"> <li>• Tachycardia disproportionate to fever, anxiety, medications</li> <li>• Bradycardia</li> <li>• CRT <math>\geq 3</math> secs, cool peripheries, cool or mottled skin, reduced peripheral pulses, narrow pulse pressure</li> <li>• Altered level of consciousness/drowsiness/irritability</li> <li>• Hypotension (a late sign in paediatric septic shock)</li> <li>• New onset end organ dysfunction</li> <li>• Evolving petechial or purpuric rash</li> <li>• Unexplained pain</li> </ul>
0 to 15 minutes	<p><b>Initial Management</b></p> <ul style="list-style-type: none"> <li>• <b>Call for help:</b> <ul style="list-style-type: none"> <li>– <b>In ED:</b> Call Consultant, move patient to <b>resuscitation room</b>. In hospital services without pediatric intensive care units, the patient is taken over by the attending physician or the on-call physician. The doctor on duty must always be requested, whose presence is strictly necessary.</li> </ul> </li> <li>• Apply <b>Oxygen</b></li> <li>• Establish <b>vascular access</b> (IV/IO)</li> <li>• Take bloods once access obtained:           <ul style="list-style-type: none"> <li>– Blood culture, lactate, acid-base profile, coagulation tests and CRP</li> <li>– <b>Do not allow blood collection to delay antibiotics/fluid more than a few minutes</b></li> </ul> </li> <li>• <b>Commence antibiotics</b> (IM antibiotics if IV/IO access not rapidly established i.e. &lt;15 mins)</li> <li>• Commence <b>fluid resuscitation</b> with sodium chloride 0.9% or Lactat Ringer 10-20 mL/kg (<b>as a push not via infusion pump</b>) for patients with suspected shock</li> <li>• <b>Correct hypoglycaemia</b> (if present) with 2 mL/kg glucose 10%. Confirm correction.</li> </ul>
15 to 60 minutes	<p><b>Ongoing resuscitation</b></p> <ul style="list-style-type: none"> <li>• Continue Fluid Resuscitation with repeat boluses of 10-20mL/kg sodium chloride 0.9% or Lactated Ringer solution as needed</li> <li>• Target reversal of shock, improved perfusion/CRT, heart rate, clinical condition</li> <li>• Monitor closely for signs of fluid overload (e.g. new onset wheeze, worsening shortness of breath, hepatomegaly)</li> <li>• Consider Balanced fluids (Lactated Ringer’s solution or Plasma-Lyte) if patient is acidotic or hyperchloremic.</li> <li>• <b>If circulatory failure persists after 40mL/kg fluid bolus:</b> <ul style="list-style-type: none"> <li>• Obtain additional vascular access. Mandatory PCC review if not already present</li> <li>• Consider peripheral inotropes after discussing with PCC and/or ED, Ward Consultant</li> <li>• Consider further fluid bolus (must be discussed with the Consultant first)</li> <li>• Prepare for intubation (particularly if altered LOC)</li> <li>• Arrange transfer to PCC</li> <li>• Consider hydrocortisone for fluid refractory, catecholamine resistant shock.</li> </ul> </li> </ul>

CRT = Capillary refill time, PCC = Pediatric Critical Care, LOC = levels of consciousness

to start treatment with inotropic/vasoactive medication must be taken after repletion with 40 (60) ml/kg in the first hour, with the opinion of the doctor on duty and always after consultation with the team members. *Epinephrine (adrenaline), considered the initial treatment of choice*, acts on  $\beta$  and  $\beta$  adrenergic receptors. In small doses, it increases heart rate, cardiac contractility and blood pressure. An option, long preferred over adrenaline, is the administration of dopamine. *Dopamine* in a dose of 5-15mcg/kg/min has an inotropic effect, increases peripheral vascular resistance and, moderates, BP [1]. Although the effects of the 2 vasoactive agents are similar, in some studies the resolution of shock was faster in the group treated with epinephrine and the mortality lower.

For the easy calculation of the quantities of inotropic/vasopressor substances, the “rule of 6” is used. In this way, the patient’s weight in kg is multiplied by 0.6 or 6, depending on the drug, and the calculated amount is included in the infusion liquid to reach a quantity of 100 ml administered through the injector.

### Correction of anemia

Red blood cell transfusion has the role of improving arterial O<sub>2</sub> saturation. The protocols recommend maintaining a level of Hb at 10 g/l, but some studies mention that values between 7.5-9 g/l did not influence mortality.

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## Corticotherapy

Different studies have shown that the administration of cortisone preparations in septic shock did not improve hemodynamic performance, increased the positivity rate of bacterial cultures, prolonged the duration of antibiotic treatment and increased mortality [20]. Indications for corticotherapy in adrenal insufficiency due to purpura fulminans are maintained, in patients under chronic treatment with cortisone preparations, congenital/acquired adrenal insufficiency [20]. Most of the pediatric intensivists still believe that steroids are necessary in hypotensive patients who do not respond to volume repletion and catecholamine treatment [21].

## Transfer to definitive care

”After resuscitation children with septic shock should be managed by clinicians with pediatric critical care expertise in a setting that has the necessary resources to provide pediatric intensive care” According to Weiss and Pomerantz, 2018 [13].

**TABLE 11.** Clinical therapeutic endpoints. Cummings, 2016 [23]

– Heart Rate normalized for age
– Capillary refill <2 sec
– Normal pulse quality
– Warm extremities
– Blood pressure normal for age
– Urine output >1ml/Kg/h
– Normal mental status

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