Septic shock in children: Rapid recognition and initial resuscitation (first hour)

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INTRODUCTION

— The early recognition and initial management of severe sepsis and septic shock in children during the critical first hour of resuscitation are reviewed here.

The definitions, epidemiology, and clinical manifestations of sepsis in children, ongoing management of children with septic shock, and the evaluation and management of neonatal shock are discussed separately.

- (See "Systemic inflammatory response syndrome (SIRS) and sepsis in children: Definitions, epidemiology, clinical manifestations, and diagnosis" and "Septic shock in children: Ongoing management after resuscitation".)
- (See "Neonatal shock: Etiology, clinical manifestations, and evaluation" and "Neonatal shock: Management".)

DEFINITIONS

— In 2005, the International Pediatric Consensus Conference defined sepsis in children as two or more of the criteria for the systemic inflammatory response syndrome (SIRS) (table 1) due to a suspected or proven infection. (See "Systemic inflammatory response syndrome (SIRS) and sepsis in children: Definitions, epidemiology, clinical manifestations, and diagnosis", section on 'Sepsis'.)

Severe sepsis was defined as all of the following:

- ≥2 age-based SIRS criteria
- Suspected or proven invasive infection
- Cardiovascular dysfunction, acute respiratory distress syndrome (ARDS), or ≥2 noncardiovascular organ system dysfunctions

Septic shock was defined as the subset with cardiovascular dysfunction, which includes at least one of the following:

- Hypotension
- Reliance on vasoactive drug administration to maintain a normal blood pressure
- Two or more of the following signs of inadequate tissue perfusion:
  - Prolonged capillary refill
  - Oliguria
  - Metabolic acidosis
  - Elevated blood lactate

Although these specific definitions are useful, sepsis presents as a clinical syndrome complicating severe infection that is characterized by multiple heterogeneous features including systemic inflammation, immune dysregulation, microcirculatory derangements, and end-organ dysfunction. The severity of illness for an individual patient is a continuum through which it may be clinically impossible to distinguish transitions from sepsis to severe sepsis and septic shock.

APPROACH

— Our approach is consistent with the 2020 Surviving Sepsis Campaign International Guidelines for the management of septic shock and sepsis-associated organ dysfunction in children provided by the initial resuscitation algorithm for children [1,2]. Specific management steps for facilities with access to intensive care are provided in the algorithm (algorithm 1).

RAPID RECOGNITION

— The goal of the initial phase of management for children with septic shock is to rapidly recognize those with infections who have severe sepsis (and are at risk for rapid progression to septic shock) as well as those with septic shock.

Septic shock is associated with high morbidity and mortality. In addition, delayed recognition of septic shock has repeatedly been associated with worse clinical outcomes in adults and children [3]. As an example, in a prospective cohort study of 91 infants and children presenting to community hospitals with septic shock (defined by hypotension or delayed capillary refill), each hour of

delay in initiation of appropriate resuscitation or persistence of hemodynamic abnormalities was associated with a clinically significant increased risk of death (odds ratio [OR] 1.5 and 2.3, respectively) [4]. (See "Systemic inflammatory response syndrome (SIRS) and sepsis in children: Definitions, epidemiology, clinical manifestations, and diagnosis", section on 'Definitions' and "Systemic inflammatory response syndrome (SIRS) and sepsis in children: Definitions, epidemiology, clinical manifestations, and diagnosis", section on 'Sepsis'.)

Institutional approach

— To minimize delays in recognition of severe sepsis and septic shock, each pediatric institution should develop a multidisciplinary protocol/guideline to improve early identification and treatment. The major components of the recognition bundle that are recommended by the pediatric 2020 Surviving Sepsis Campaign International Guidelines include [1,2]:

- **Systematic screening for identification of severe sepsis or septic shock** – Institutions should implement a septic shock identification/trigger tool that consists of combinations of clinical diagnoses and findings (eg, high-risk patient conditions, vital signs, and/or physical findings) that prompt further evaluation.

  The tool should be adapted to the setting and patient population where it will be used. Implementation through an electronic health record may facilitate clinician compliance. An example of an emergency department trigger tool designed for use by triage nurses and incorporating vital sign thresholds used in the Pediatric Advanced Life Support course is provided (algorithm 2). Some institutions may choose previously proposed vital sign triggers (table 1). Each institution should base their vital sign triggers on their best interpretation of the evidence and what will be most functional in their system.

- **Rapid clinical assessment for patients with possible severe sepsis/septic shock** – Once screening with the trigger tool indicates that a patient may have severe sepsis/septic shock, they should undergo rapid clinical assessment within 15 minutes by a physician, physician assistant, or advanced practice nurse to confirm findings of septic shock, implement additional monitoring, and determine the resuscitation plan.

- **Rapid initiation of resuscitation** – Resuscitation should be initiated within 15 minutes of confirming severe sepsis or septic shock. (See 'Resuscitation' below.)

Red-flag findings

— Red-flag findings that should prompt rapid clinical assessment and resuscitation for severe sepsis or septic shock include [5]:

- Presence of fever (core temperature >38.3°C [101°F] for patients three months of age and older or >38°C [100.4°F] for infants younger than three months of age)
- Hypothermia (core temperature <36°C [96.8°F])
- Tachycardia
- Tachypnea
- Abnormal pulse (diminished, weak, or bounding)
- Abnormal capillary refill (central refill ≥3 seconds or flash refill [<1 second])
- Hypotensive
- Abnormal mental status:
  - Irritability
  - Inappropriate crying
  - Inappropriate drowsiness (eg, excessive per caregiver)
  - Not interacting with caregiver
  - Difficult to arouse (lethargic or obtunded)
  - Confused (not oriented to person, place, or time when developmentally appropriate to test)
- Purpura anywhere on the body or petechiae below the nipple line (picture 1 and picture 2)
- Macular erythema (picture 3 and picture 4) with mucosal changes (eg, strawberry tongue and conjunctival injection (picture 5)) suggestive of toxic shock syndrome

Tachycardia and tachypnea are common and nonspecific findings in young pediatric patients and may be due to fever, anxiety, dehydration, pain/discomfort, anemia, or agitation. In febrile children, the heart rate may be adjusted by deducting approximately 10 beats per minute for every 1°C (1.8°F) elevation in temperature. However, tachycardia should resolve when the temperature returns to normal; persistent sinus tachycardia is a sensitive indicator of circulatory dysfunction and should **not** be overlooked. (See "Approach to the child with tachycardia", section on 'Vital signs'.)

Clinicians must appreciate that hypotension is a late sign of cardiovascular dysfunction and shock in pediatric patients and is **not** necessary to diagnose septic shock. Infants and children with sepsis often maintain blood pressure despite the presence of septic shock through an increase in heart rate, systemic vascular resistance, and venous tone but have a limited capacity to augment myocardial stroke volume. As a result, infants and children may be more likely to exhibit "cold" shock in sepsis compared with the classic presentation of "warm" (or hyperdynamic/vasodilated) shock in adults. (See "Systemic inflammatory response syndrome (SIRS) and sepsis in children: Definitions, epidemiology, clinical manifestations, and diagnosis", section on 'Shock'.)

Rapid resuscitation that is tailored to the patient's clinical condition and to the presence or absence of intensive care services should

be started in patients with red-flag findings for sepsis or septic shock. (See 'Resuscitation' below.)

Signs and symptoms of infection

— In addition to the red-flag findings listed above, signs and symptoms of infection support the clinical suspicion of septic shock. Common clinical findings found in children with sepsis and septic shock include:

- Toxic or ill appearance
- Signs of dehydration (table 2)
- Rigors
- Decreased tone in neonates and infants
- Seizures
- Meningismus
- Respiratory depression or failure
- Pulmonary rales or decreased breath sounds caused by bronchopneumonia
- Distended, tender abdomen (eg, perforated viscus or intraabdominal abscess)
- Costovertebral angle tenderness (eg, pyelonephritis)
- Macular erythema (toxic shock syndrome)
- Skin cellulitis, lymphangitis, or abscess (picture 6)
- Warmth, swelling, and/or erythema of an extremity or joint suggestive of osteomyelitis and/or septic arthritis
- Peripheral edema caused by capillary leak
- Multiple nodules that can be seen with disseminated *Staphylococcus aureus* or fungal infections (picture 7)
- Ecthyma associated with *Pseudomonas* infection (picture 8 and picture 9)
- Purpura associated with *Neisseria meningitidis* and *Streptococcus pneumoniae* as well as other bacterial etiologies

RESUSCITATION

Institutional guidelines and protocols

— Each institution should develop a multidisciplinary approach to the resuscitation of pediatric patients with severe sepsis or septic shock that codifies the time-limited stabilization tasks recommended within the first few hours of treatment by the Surviving Sepsis Campaign [1,2].

Institutional implementation of resuscitation protocols and guidelines with transparent goals can improve adherence to best practices, decrease time to therapy, and improve outcomes in pediatric septic shock [3,6,7]. As an example, in an observational study that compared outcomes before and after implementation of a sepsis resuscitation protocol, time from triage to receipt of the first fluid bolus significantly decreased from a median of 56 to 22 minutes and from triage to the first antibiotic from a median of 130 to 30 minutes [6]. In another study that evaluated the impact of specific quality improvement interventions in a pediatric emergency department, adherence to timely performance of essential actions within 60 minutes of recognition quadrupled (from 19 to 78 percent) [7]. The essential actions consisted of:

- Recognition of septic shock
- Vascular access and rapid fluid resuscitation
- Empiric antimicrobial therapy
- Initiation of vasoactive agents to patients not responding sufficiently to fluid resuscitation

This improvement in guideline adherence was associated with a decrease in mortality from 5 to 2 percent.

Approach

— The approach provided in this topic is largely consistent with goal-targeted therapy for pediatric septic shock recommended by the 2020 Surviving Sepsis Campaign guidance provided in the initial resuscitation algorithm for children [1,2]. Goal-targeted therapy for septic shock refers to an aggressive systematic approach to resuscitation aimed at improving physiologic indicators of perfusion and vital organ function within the first few hours of care. Timing is determined by whether the child has septic shock or sepsis:

- **Septic shock** – For children with septic shock, for whom clinical recognition of abnormal perfusion or hypotension is typically evident without the need for additional laboratory testing, the following six management steps should be accomplished within **one hour** of recognition (algorithm 2 and algorithm 1) [1,2]:
    - Obtain intravenous (IV)/intraosseous (IO) access.
    - Collect blood culture (before antibiotics are administered whenever possible).
    - Start broad-spectrum, empiric antimicrobial therapy.
    - Measure blood lactate (if available).
    - Fluid therapy:
        - In health care settings **with** access to mechanical ventilation, ongoing hemodynamic assessment, and other aspects of intensive care (either locally or through interhospital transport irrespective of whether this care is provided in a formal intensive care unit [ICU] or not), administer a fluid bolus of 10 to 20 mL/kg if shock is present and provide further fluid resuscitation depending upon patient condition and response. (See 'Facilities with access to intensive

care' below.)

- In health care settings **without** access to mechanical ventilation, ongoing hemodynamic assessment, and other aspects of intensive care (either locally or through interhospital transport irrespective of whether this care is provided in a formal ICU or not), fluid bolus therapy should **not** be administered routinely unless the patient has severe hypotension or World Health Organization (WHO)-defined circulatory impairment (cold extremities with prolonged capillary refill >3 seconds and weak, fast pulse). (See 'Resource-limited settings' below.)

- Start vasoactive agents if shock persists after 40 to 60 mL/kg (or sooner if signs of fluid overload develop or myocardial dysfunction is present).

Additional goals within the first hour are to [5]:

- Maintain or restore airway, oxygenation, and ventilation.
- Assess cardiac function.
- Reassess hemodynamic response to fluid and/or vasoactive therapy.

- **Sepsis** – For children with suspected sepsis but without clinical evidence of shock, the same management steps are recommended if an expedited diagnostic evaluation supports the diagnosis of sepsis. Both the expedited diagnostic evaluation, which includes additional laboratory and clinical testing to assess for infection and organ dysfunction, and initiation of the above management steps should occur within **three hours** of initial suspicion of sepsis (but start as soon as sepsis is evident) [1,2].

Restoration of tissue perfusion and reversal of shock is identified by the following therapeutic endpoints (goals below in parentheses)

[5,8,9]:

- Quality of central and peripheral pulses (strong, distal pulses equal to central pulses)
- Skin perfusion (warm, with capillary refill <2 seconds)
- Mental status (normal mental status)
- Urine output (≥1 mL/kg/hour, up to 40 mL/hour, once effective circulating volume is restored)
- Blood pressure (systolic pressure at least fifth percentile for age):
  - <1 month of age: 60 mmHg
  - 1 month to 10 years of age: 70 mmHg + [2 x age in years]
  - 10 years of age and older: 90 mmHg

  However, blood pressure by itself is not a reliable end point for assessing the adequacy of resuscitation.
- Normal serum lactate (eg, <2 mmol/L)
- Central venous oxygen saturation ($ScvO_2$) ≥70 percent, if available and appropriate (invasive monitoring may not be needed in patients who rapidly respond to initial resuscitation); this target is **not** applicable to children with congenital heart disease characterized by mixing lesions

Heart rate is an important physiologic indicator of circulatory status that should also be monitored closely. However, many other factors (ie, fever, drugs, anxiety) influence heart rate. Although trends in response to treatment should be carefully monitored, specific target goals for heart rate are difficult to define and may **not** be useful. Children with persistently elevated heart rate unresponsive to repeated fluid boluses should be evaluated for cardiac dysfunction. (See 'Red-flag findings' above.)

Blood lactate can be obtained by bedside testing. Limited evidence suggests that serum lactate that decreases with treatment within two to four hours is associated with better outcomes for children with sepsis. In our practice, our therapeutic target is <2 mmol/L. Small observational studies in children have demonstrated that lactate can correlate with severity of shock and prognosis in sepsis [10-12]. In one observational study of septic shock in children, normalization of lactate (blood lactate <2 mmol/L) within four hours was associated with reduced organ dysfunction, but lactate clearance (reduction ≥10 percent decrease in lactate level) was not [11]. In adults, normalization of lactate and lactate clearance have been associated with decreased mortality. (See "Evaluation and management of suspected sepsis and septic shock in adults", section on 'Initial investigations' and "Evaluation and management of suspected sepsis and septic shock in adults", section on 'Laboratory'.)

Except in patients with congenital heart disease with mixing lesions, $ScvO_2$ <70 percent may also indicate persistence of abnormal end-organ perfusion. However, an $ScvO_2$ ≥70 percent can be falsely reassuring in sepsis due to hyperdynamic cardiac function, microcirculatory shunting, or mitochondrial dysfunction [13,14]. When measuring $ScvO_2$ in pediatric patients, pulmonary artery catheters are rarely used. Instead, changes in $ScvO_2$ are more commonly obtained from a catheter with its tip in the distal superior vena cava [15].

Identifying physiologic indicators to monitor the effectiveness of resuscitation for children with septic shock is challenging. Noninvasive ultrasonic determination of cardiac index, cardiac output, systemic vascular resistance, and stroke volume is feasible in healthy children, and age-based normative values have been published. Although not widely available, bedside Doppler ultrasound shows promise as a noninvasive method to guide vasoactive therapy by calculating cardiac output and systemic vascular resistance

from measurements of blood flow over the pulmonary artery or aorta. (See "Initial management of shock in children", section on 'Clinical and physiologic targets'.)

Regardless of the method used to measure blood pressure, clinical signs of end-organ perfusion must also be monitored in order to accurately determine the severity of shock and response to treatment. These indicators can be readily monitored noninvasively during the initial management of shock, and (since many children in shock respond well) invasive monitoring can often be avoided. Mean arterial pressure can be measured with a blood pressure cuff. Clinical experience suggests that quality of central and peripheral pulses, skin perfusion, mental status, and urine output are useful signs for assessing response to therapy. Limited observational evidence suggests that capillary refill time may correlate with $ScvO_2$. (See "Initial management of shock in children", section on 'Clinical and physiologic targets'.)

These timelines are proposed as a goal because observational studies suggest that outcomes among children with septic shock are improved when these goals are met. For example, among 1179 children with sepsis across 54 hospitals in New York (United States), completion of a sepsis bundle within one hour was associated with lower risk-adjusted odds ratio (aOR) of in-hospital mortality (0.59, 95% CI 0.38-0.93) [3]. In a single-institution study, bundle-compliant care in 1380 children with septic shock was associated with five times lower mortality (odds ratio [OR] 0.20, 95% CI 0.07-0.53) [16]. In another study, implementation of a sepsis protocol led to a substantial reduction in the proportion of children who no longer had organ dysfunction on day two after presentation (aOR 4.2, 95% CI 1.7-10.4) [17]. However, these timeframes are not always achievable depending upon resources available. Furthermore, individual patients can have good outcomes despite these time limits not being met.

All patients

— All patients with suspected septic shock should receive continuous monitoring of heart rate, breathing, and pulse oximetry and frequent measurements of blood pressure, timely support of airway and breathing, and rapid fluid resuscitation [5]. Further treatment is determined by the initial response to fluid resuscitation.

Airway and breathing

— Patients with septic shock should initially receive supplemental oxygen to optimize blood oxygen content and, thus, oxygen delivery to tissues if they present with or develop hypoxemia. Oxygenation should be monitored using continuous pulse oximetry.

Although evidence is lacking in children, we support titration of supplemental oxygen, as needed, to assure oxygen saturation (SpO_2) 92 to 97 percent and to avoid SpO_2 >97 percent. This approach may prevent the adverse effects (eg, lung injury and microcirculatory vasoconstriction) associated with hyperoxia and free radical generation [18]. (See "Continuous oxygen delivery systems for the acute care of infants, children, and adults".)

In children who are responding to initial resuscitation without a clear indication for intubation, a trial of noninvasive ventilation such as continuous positive airway pressure ventilation or bilevel positive airway pressure ventilation is suggested, particularly in those with pediatric acute respiratory distress syndrome [19-21]. (See "Noninvasive ventilation for acute and impending respiratory failure in children".)

Endotracheal intubation using rapid sequence intubation (RSI) is frequently necessary in children with fluid-refractory, catecholamine-resistant septic shock to protect the airway, assist with ventilation, and/or promote oxygenation. In addition, endotracheal intubation and sedation reduce the work of breathing, which may avoid diversion of cardiac output to the muscles of respiration and may improve perfusion to other organs. A rapid overview of RSI in children is provided in the table (table 3). Emergency endotracheal intubation in children and pediatric RSI are discussed in detail separately. (See "Emergency endotracheal intubation in children" and "Rapid sequence intubation (RSI) outside the operating room in children: Approach".)

When performing RSI in children with septic shock, key actions include [5]:

- Patients with hemodynamic instability should receive appropriate support with fluid and/or catecholamines prior to or during intubation. (See 'Fluid resuscitation' below and 'Patients with fluid-refractory shock' below.)
- Pretreatment with atropine is suggested in infants and younger children to counteract reflex bradycardia that may progress to progressive, unstable bradycardia during RSI. (See "Rapid sequence intubation (RSI) outside the operating room in children: Approach", section on 'Pretreatment'.)
- Ketamine, if available and **not** contraindicated (eg, patients younger than three months of age or with schizophrenia), is suggested for sedation prior to endotracheal intubation. (See "Rapid sequence intubation (RSI) outside of the operating room in children: Medications for sedation and paralysis", section on 'Ketamine'.)
- Etomidate inhibits cortisol formation and is not recommended unless ketamine is not available or is contraindicated by psychosis. Fentanyl in doses of 1 to 2 mcg/kg given slowly is suggested for infants younger than three months of age.
- Short-acting barbiturates and propofol are associated with hypotension and should be **avoided** in children with septic shock.

When performing RSI in a child with septic shock, it is important to choose agents that do not worsen cardiovascular status. Previously, etomidate was a common choice because it typically does not compromise hemodynamic stability. However, small observational studies in children with sepsis and septic shock undergoing intubation with or without etomidate indicate that one dose of etomidate is associated with lower levels of serum cortisol, lower cortisol to 11-deoxycortisol ratios, and higher adrenocorticotropic hormone levels for up to 24 hours [22,23]. In one case series of 31 children with meningococcal sepsis who required endotracheal intubation, of the eight children who died, seven received etomidate [23].

Circulation

Establish venous access

— IV access (preferably two sites and of the largest caliber that can be reliably inserted) should be established within five minutes in patients with septic shock.

If a peripheral IV cannot be obtained in this time, placement of an IO needle is indicated. (See "Vascular (venous) access for pediatric resuscitation and other pediatric emergencies", section on 'Peripheral access' and "Intraosseous infusion", section on 'Indications' and "Intraosseous infusion", section on 'Fluid and drug administration'.)

Obtain laboratory studies

— Suggested laboratory studies for children with sepsis and septic shock should be obtained as vascular access is achieved and include (see "Systemic inflammatory response syndrome (SIRS) and sepsis in children: Definitions, epidemiology, clinical manifestations, and diagnosis", section on 'Laboratory studies'):

- Rapid blood glucose
- Venous or arterial blood gas
- Complete blood count with differential
- Blood culture
- Blood lactate
- Serum electrolytes
- Blood urea nitrogen and serum creatinine
- Ionized blood calcium
- Serum total bilirubin
- Alanine aminotransferase (ALT)
- Prothrombin time (PT)
- Partial thromboplastin time (PTT)
- International normalized ratio (INR)
- Fibrinogen and D-dimer
- Urinalysis
- Urine culture
- Other cultures as indicated by clinical findings
- Serologic testing as indicated to identify suspected sources of infection
- Inflammatory biomarkers (eg, C-reactive protein, procalcitonin) in selected cases (such as children with fever and central lines, community-acquired pneumonia, and infants younger than two months of age) [24-28]. However, some experts draw inflammatory biomarkers in all patients to aid in assessment of adequacy of antimicrobial treatment and source control.

The following abnormal laboratory findings are often reported in children with septic shock:

- Lactic acidosis indicated by metabolic acidosis on blood gases and elevation of arterial blood lactate (>2 mmol/L) (see "Systemic inflammatory response syndrome (SIRS) and sepsis in children: Definitions, epidemiology, clinical manifestations, and diagnosis", section on 'Laboratory studies')
- Age-specific leukocytosis or leukopenia (table 1)
- Platelet count <80,000/microL or a decline of 50 percent from highest value recorded over the past three days
- Disseminated intravascular coagulopathy (decreased fibrinogen with increased D-dimer, INR, PT, or PTT) (see "Disseminated intravascular coagulation in infants and children", section on 'Diagnosis')
- Renal insufficiency suggested by a serum creatinine ≥2 times upper limit of normal for age or twofold increase in baseline creatinine
- Liver dysfunction implied by a total bilirubin ≥4 mg/dL (not applicable to newborn) or ALT >2 times upper limit of normal for age
- Pyuria indicating an urinary tract infection

Additional discussion of the interpretation of laboratory findings in children with septic shock is provided separately. (See "Systemic inflammatory response syndrome (SIRS) and sepsis in children: Definitions, epidemiology, clinical manifestations, and diagnosis", section on 'Laboratory studies'.)

Treat hypoglycemia — — Children with septic shock are at risk for hypoglycemia; rapid blood glucose should be measured as IV access is obtained. If present, hypoglycemia should be corrected by rapid IV infusion of dextrose as described in the rapid overview (table 4).

After initial hypoglycemia is reversed, the clinician should continue to monitor blood glucose. Maintaining a blood glucose <180 mg/dL (8.33 mmol/L) is desirable. Hypoglycemia may also be an indicator of adrenal insufficiency in predisposed children and those with refractory septic shock. (See 'Patients at risk for adrenal insufficiency' below and 'Patients with catecholamine-resistant shock' below.)

In normoglycemic young children, a continuous maintenance infusion of dextrose 5 to 10 percent in addition to resuscitation fluids is a reasonable option to prevent the occurrence of hypoglycemia [5].

Treat hypocalcemia — — Children with septic shock are at risk for hypocalcemia [29]; serum ionized calcium should be measured as IV access is obtained. Our practice is to monitor ionized blood calcium levels every one to two hours during initial

management of septic shock.

For patients with a serum ionized calcium <1.1 mmol/L (4.8 mg/dL) and either symptomatic hypocalcemia (eg, positive Chvostek or Trousseau signs, seizures, prolonged QT interval on electrocardiogram, or cardiac arrhythmias) or septic shock who require vasoactive medications, we suggest treatment with IV calcium. The suggested dose is calcium gluconate, 10 percent solution, 50 mg/kg (0.5 mL/kg), maximum dose 2 g (20 mL) by slow IV or IO infusion over five minutes. This suggested dose is equivalent to elemental calcium 5 mg/kg (0.15 mmol/kg), up to 180 mg elemental (4.5 mmol) per single dose [1,2].

Calcium chloride 10 percent in a dose of 10 to 20 mg/kg (0.1 to 0.2 mL/kg), maximum dose 1 g (10 mL) provides an equivalent dose but should **only** be administered through a central line unless the patient develops impending or actual cardiac arrest.

Patients receiving a calcium infusion warrant continuous cardiac monitoring. Calcium should be administered in a larger vein or, preferably, a central line. Sodium bicarbonate should **not** be introduced into an IV or IO cannula without flushing before and after administration because of potential precipitation.

Although definitive evidence to support improved clinical outcomes in humans receiving IV calcium for low ionized calcium levels is lacking [2,30], hypocalcemia is a common finding in critically ill children with sepsis likely due to changes in the hormonal milieu, though the exact pathophysiology remains unclear [29]. Intracellular calcium is necessary for cardiac and smooth muscle contraction. Infants under 12 months of age may rely more heavily on extracellular calcium to maintain adequate cardiac contractility than older patients. Animal models and observational studies have suggested improved physiologic outcomes when hypocalcemia is treated [31,32].

Fluid resuscitation

— For infants and children with septic shock, rapid fluid resuscitation is an essential treatment that should not be delayed. Relative intravascular hypovolemia is common in septic shock (due to vasodilation and capillary leak) and may be severe. The major goal for the initial treatment of septic shock consists of rapid fluid resuscitation to restore tissue perfusion based upon clinical therapeutic endpoints (eg, improvement of quality of pulses, capillary refill time, mental status, urine output) as provided by the initial resuscitation algorithm for children [5,8,9].

The approach to fluid resuscitation in extremely preterm infants (<28 weeks gestational age) is discussed separately. (See "Neonatal shock: Management" and "Neonatal shock: Management", section on 'Fluid resuscitation'.)

Facilities with access to intensive care — — For children with septic shock treated in settings with access to acute intensive care capability (either locally or via interhospital transport, and whether or not this care can be provide in a formal ICU), patients without signs of fluid overload should receive 10 to 20 mL/kg of balanced crystalloid solution such as lactated Ringer's solution; 0.9% normal saline is an acceptable alternative if lactated Ringer's is not available (algorithm 1) [5]. Fluid volume should be calculated based upon ideal body weight (eg, 50th percentile for age (figure 1A-B and figure 2A-B)). Infusion of this amount of fluid over 5 to 10 minutes can be achieved with a manual "push-pull" technique or rapid infuser. Use of a time clock has facilitated the timely administration of fluids in at least one setting [7].

If the patient develops signs of fluid overload (eg, rales, worsening respiratory distress, new or worsening oxygen requirement, gallop rhythm, hepatomegaly, or cardiomegaly or pulmonary edema on chest radiograph), further fluid bolus administration should be omitted or reduced (eg, 5 to 10 mL/kg given over 15 minutes) and continued septic shock treated with vasoactive infusions (see 'Indications for vasoactive agents' below). Patients with signs of fluid overload who continue to receive fluid boluses warrant close monitoring for respiratory and cardiac failure. The clinician should have a low threshold for endotracheal intubation and mechanical ventilation to treat pulmonary edema in these patients.

After the initial infusion, the child should be quickly reassessed for signs of inadequate end-organ perfusion to determine if additional fluid is needed and to identify any signs of fluid overload (eg, pulmonary rales or gallop rhythm). The clinical and hemodynamic response and the presence or absence of volume overload must be assessed before and after each bolus. (See 'Red-flag findings' above and "Initial management of shock in children", section on 'High-risk conditions'.)

Within the first hour of treatment, the physician should determine if the patient is responding to timely fluid administration or not. Patients who are fluid refractory (ie, no improvement or worsening despite crystalloid fluid resuscitation with 40 to 60 mL/kg) warrant vasoactive therapy (eg, continuous infusion of epinephrine (table 5 and table 6) or norepinephrine) tailored to blood pressure. (See 'Patients with fluid-refractory shock' below.)

In addition, as long as each fluid bolus provides hemodynamic improvement, fluid resuscitation should still continue until tissue perfusion, oxygen delivery, and blood pressure are adequate or signs of fluid overload (rales, gallop rhythm, enlarged liver) develop regardless of the use of vasoactive infusions. Experience suggests that patients with septic shock can require volumes of up to 60 mL/kg in the first hour, and some receive 120 mL/kg or more during the first several hours of fluid administration [33,34]. Evidence is lacking to determine if earlier initiation of vasoactive therapy reduces or eliminates the need for large-volume fluid resuscitation and decreases adverse effects increasingly reported with fluid overload.

Achievement of targets for timely fluid resuscitation has been associated with reduction in mortality without negative impact on resource utilization [7,16] (see 'Outcomes' below). However, despite institution-wide focus on the treatment of septic shock in these studies, the fluid resuscitation goal is not always met, even in these highly-resourced settings. The feasibility of a one-hour target for fluid resuscitation has not been addressed outside of tertiary care pediatric institutions.

Our suggestion in favor of balanced crystalloid solution instead of normal saline is based largely on indirect evidence in adults that resuscitation fluids with high chloride concentrations such as normal saline are associated with more adverse outcomes than balanced crystalloid fluids, especially for patients in septic shock. (See "Evaluation and management of suspected sepsis and septic shock in adults", section on 'Choice of fluid'.)

In children, observational studies are inconsistent with respect to the benefit of resuscitation with balanced crystalloid solutions [35,36]. In one retrospective observational study that used propensity-matched data from a national registry of almost 37,000 children with severe sepsis, exclusive resuscitation with balanced crystalloid fluids for the first 72 hours was associated with a shorter duration of vasoactive infusions, less acute kidney injury, and significantly lower mortality compared with normal saline [35]. However, in a second observational study that used data from insurance records and matched over 2000 children who received balanced crystalloid solution 1:1 with children who received normal saline, mortality, likelihood of acute kidney injury, and length of hospital or intensive care unit stay were similar in both groups [36].

In our practice, we generally use a crystalloid solution instead of albumin solution because of the lack of clear benefit and higher cost of albumin. (See "Initial management of shock in children", section on 'Type of fluid'.)

For children with hypoalbuminemia (albumin <3 g/dL), or those who develop a hyperchloremic metabolic acidosis, colloid infusion with albumin 5% is a reasonable option.

Although the findings are not consistent and multiple preparations are available, synthetic colloids, such as hydroxyethyl starch solutions, as well as gelatin-derived fluids should be **avoided** because they have been shown to increase the risk of acute kidney injury, coagulopathy, and death in adults with severe sepsis or septic shock, especially administered in volumes >15 mL/kg. (See "Treatment of hypovolemia (dehydration) in children", section on 'Crystalloid versus colloid' and "Evaluation and management of suspected sepsis and septic shock in adults", section on 'Intravenous fluids (first three hours)'.)

Preliminary evidence in one small pediatric trial suggests that administration of hypertonic saline may achieve hemodynamic stability with a lower volume of fluid, but its impact on other outcomes relative to normal saline are uncertain [37]; thus, we do **not** advocate use of hypertonic saline outside of an experimental protocol.

Resource-limited settings — — In resource-limited settings without access to intensive care with advanced airway and circulatory support (whether outside or inside of a formal intensive care unit setting), treatment of sepsis and septic shock should be modified based on WHO guidelines. Diagnosis of shock (septic or otherwise) per WHO criteria requires the presence of all three of the following: cold extremities, prolonged capillary refill >3 seconds, and weak/fast pulse. Measurement of blood pressure is not required. Severe sepsis is defined as the presence of fewer than three of these features [1,2,38].

- **Severe sepsis** – Children in resource-limited settings with severe sepsis should receive maintenance fluids rather than boluses in the absence of hypotension or WHO criteria for circulatory impairment (cold extremities **with** prolonged capillary refill >3 seconds **and** weak, fast pulse). In children with signs of compensated shock and severe febrile illness but **without** dehydration, burns, or hemorrhage, rapid bolus administration of albumin or normal saline increases mortality [39].

- **Septic shock** – In patients in resource-limited settings with septic shock and **without** severe anemia (hemoglobin <5 g/dL [hematocrit <15 percent]) or severe acute malnutrition, WHO guidelines suggest judicious administration of bolus fluids in aliquots of 10 to 20 mL/kg over the first 30 to 60 minutes. For children who remain in shock, an additional 10 mL/kg over 30 minutes may be given [38].

  The approach in the first hour should be modified for those with severe anemia or severe malnutrition as follows:

  - Patients with septic shock and hypotension accompanied by severe anemia should receive a blood transfusion before crystalloid solutions, if possible.

  - Patients with septic shock and hypotension accompanied by severe acute malnutrition may receive 10 to 15 mL/kg of balanced crystalloid solution over the first hour.

  Fluid resuscitation should be titrated to cardiac output and discontinued if the patient develops clinical signs of fluid overload [1,2]. Although current guidelines recommend rapid administration of fluid to children with septic shock using a "push-pull" technique, the safety of this practice has been questioned by some studies in resource-limited settings. For example, in a small trial performed in India, children with septic shock who were largely underweight for age were more likely to be intubated in the first 24 hours if they were randomized to fluid boluses over 5 to 10 versus 15 to 20 minutes. However, resolution of shock and mortality were the same in both groups, and a definitive conclusion regarding the role of rapid fluid resuscitation in causing a greater need for mechanical ventilation was limited by the small sample size, lack of central randomization, and lack of blinding [40,41]. Still, in light of evidence regarding potential harm from rapid fluid resuscitation in patients with severe febrile illness in resource-limited settings, we advise caution with both volume and speed of fluid boluses if access to mechanical ventilation is limited and life-threatening shock is not present.

Patients with dehydration or ongoing fluid losses, (eg, diarrhea or severe capillary leak as with dengue shock syndrome) should receive fluid therapy according to the WHO Emergency Triage Assessment and Treatment guidelines (table 7). (See "Dengue virus infection: Prevention and treatment", section on 'Management of plasma leakage'.)

The fluid expansion as support therapy (FEAST) trial, a randomized trial of 3141 children between 60 days and 12 years of age with severe febrile illness (altered mental status, respiratory distress, or both) and impaired perfusion (eg, delayed capillary refill time ≥ 3 seconds, weak pulses, or severe tachycardia) treated in six district hospitals in sub-Saharan Africa found that 48-hour mortality was significantly higher among those who received boluses of albumin or normal saline when compared with controls who did not receive fluid boluses (10.6 or 10.5 versus 7.3 percent, respectively) [39,42]. These children had a high frequency of malaria parasitemia (57 percent) and severe anemia (hemoglobin <5 g/dL, 32 percent) although preplanned subgroup analyses did not find a difference in mortality based upon these characteristics. More children in the no fluid bolus group received blood transfusions in the first hour than in the fluid bolus groups (22 versus 2 to 4 percent). However, the overall amount of blood delivered after eight hours was not significantly different among the groups. A subsequent re-analysis of this study found that cardiovascular collapse from cardiotoxicity or ischemia-reperfusion injury in patients receiving fluids accounted for the excess mortality rather than fluid

overload [43,44].

Of note, none of the patients in this trial had hypovolemic dehydration or trauma as the primary cause of their illness, and patients with severe hypotension received 40 mL/kg of normal saline or albumin. Such patients still warrant fluid resuscitation according to the WHO guidelines. (See "Initial management of shock in children", section on 'Resource-limited settings'.)

Although the FEAST trial is the only randomized trial of fluid therapy in children with compensated septic shock, it indicates a potential for significant harm if fluid therapy is used indiscriminately among children with severe febrile illness in resource-limited settings. There is no evidence that these findings can be generalized to resource-rich settings where the baseline characteristics of the patients are significantly different and intensive monitoring, mechanical ventilation, and vasopressor support are routinely available. However, limited observational evidence suggests that even in clinical facilities with these capabilities, early isotonic fluid resuscitation (eg, normal saline or lactated Ringer's solution) should be carefully guided by the response to bolus therapy as well as the degree and type of shock present. (See "Initial management of shock in children", section on 'Clinical and physiologic targets' and "Initial management of shock in children", section on 'Resource-limited settings' and "Initial management of shock in children", section on 'Volume and rate'.)

Blood transfusion

— In hemodynamically unstable children with septic shock (eg, profound hypotension, persistence of lactate >2 mmol/L, progressive/persistent end-organ dysfunction, and/or $ScvO_2$ <70 percent despite high levels of vasopressor support or profound hypoxia), we suggest blood transfusion to maintain a hemoglobin threshold of 9 g/dL [1,2]. For hemodynamically stable children who are not bleeding, the minimum safe threshold is 7 g/dL. (See "Septic shock in children: Ongoing management after resuscitation", section on 'Blood transfusion'.)

Monitoring

— Once effective circulating volume has been restored, ongoing fluid requirements are guided by monitoring of tissue perfusion, including (see "Septic shock in children: Ongoing management after resuscitation", section on 'Ongoing and invasive monitoring'):

- Mean arterial blood pressure target >5^{th} percentile for age
- Capillary refill time
- Urine output
- Replacement of measured or estimated fluid losses
- Serial blood lactate levels
- If available and appropriate, measurement of:
    - Arterial blood pressure
    - Central venous pressure
    - $ScvO_2$

The mean arterial pressure target can be estimated as follows: mean arterial pressure (5^{th} percentile at 50^{th} height percentile) > 1.5 x age in years + 40 [45].

Empiric antibiotic therapy

— Prompt identification and treatment of the site(s) of infection are the primary therapeutic interventions for septic shock, with most other interventions being purely supportive. Blood cultures should be obtained prior to initiating antibiotic therapy as long as they are obtained without delaying antibiotic administration.

Timing

— For children with septic shock, broad-spectrum IV antibiotic therapy should begin within one hour of presentation, preferably after obtaining appropriate cultures. Effective delivery of antibiotics usually requires two ports or sites for IV access: one devoted to fluid resuscitation and one for antimicrobial delivery.

Antibiotics should **not** be withheld for children in whom lumbar puncture cannot be performed safely due to hemodynamic instability or coagulopathy (table 8). If obtaining blood cultures is difficult, it should not impede antibiotic initiation within the first hour. As discussed below, antifungal and antiviral agents should be included as part of the initial regimen for susceptible patients.

The rationale for the one-hour target for antimicrobial administration comes from observational studies that show poor outcomes with delays in antibiotic therapy, even beyond just one hour. In one pediatric series of 130 patients with severe sepsis or septic shock, delays greater than three hours were associated with significantly increased odds of mortality (OR 4.0 [95% CI 1.3-12.1]) [46]. In another prospective observational study, mortality from septic shock was 1 percent among children who met goals for timely administration of fluids within one hour and antibiotics within three hours versus 4 percent for those who did not (adjusted odds of death 0.2, 95% CI 0.07-0.53) [16]. Each hour delay in antibiotic administration has been associated with an approximately 8 percent increase in mortality in adults. (See "Evaluation and management of suspected sepsis and septic shock in adults", section on 'Timing'.)

Despite institution-wide focus on the treatment of septic shock in these studies, the goal of administering antibiotic therapy within one hour is not always met, even in highly resourced settings. The feasibility of a one-hour target for empiric antibiotic therapy has not been addressed outside of tertiary care pediatric institutions.

In patients with sepsis-associated organ dysfunction **without** shock, antibiotics should be given as soon as possible but within three hours of implementation of resuscitation protocol/guidelines.

For patients with suspected sepsis but without clinical shock, an expedited diagnostic evaluation to assess for likely infection or

presence of organ dysfunction can reduce unnecessary antibiotic therapy. In one pediatric study, mortality was significantly increased only when antimicrobials were administered >3 hours in comparison to <3 hours, whereas the mortality of patients receiving antimicrobials within <1 hour was not statistically different from those receiving antimicrobials within <3 hours [46]. A second, larger pediatric study demonstrated a significant decrease in mortality if antimicrobials were administered within one hour, but only in the context of a bundle that included a blood culture and fluid bolus [3].

Thus, available pediatric studies do not provide a clear time cutoff after which the risk of mortality or other adverse outcomes increases but rather support that there is likely to be an incremental risk for harm as time to antimicrobial initiation increases (in particular, beyond three hours). Thus, while antibiotics should be administered **as soon as possible** after sepsis recognition, it is reasonable to first perform a diagnostic investigation when **clinical signs of shock** are not present and the diagnosis of sepsis is uncertain. If and when the evaluation supports a likely infection or sepsis (or shock develops during the evaluation), antibiotics should be immediately administered.

Empiric regimens — Empiric antibiotics should be broad spectrum and cover all likely pathogens. The choice of antimicrobials can be complex and should consider the child's age, history, comorbidities, clinical syndrome, Gram stain data, and local resistance patterns. Consultation with an expert in pediatric infectious disease is strongly encouraged for all children with septic shock.

General principles for initial antimicrobial coverage for children who are critically ill with severe sepsis or septic shock include the following:

- Maximize the antimicrobial dose by using dosing recommended for severe infection for each administered drug.
- Antimicrobials that cover against the same organism should not be routinely administered to immunocompetent patients.
- Multidrug therapy is recommended in immunocompromised patients or immunocompetent patients at high risk for multidrug-resistant pathogens.
- Children with septic shock at risk for methicillin-resistant *Staphylococcus aureus* (MRSA) due to either high community prevalence or personal/family history of MRSA should receive empiric vancomycin or an alternative agent.
- Coverage for enteric organisms should be added whenever clinical features suggest genitourinary and/or gastrointestinal sources (eg, perforated appendicitis or bacterial overgrowth in a child with short gut syndrome).
- Treatment for *Pseudomonas* species should be included for children who are immunosuppressed or at risk for infection with these organisms (ie, neutropenic patient).
- Listeria monocytogenes and herpes simplex virus (HSV) are important pathogens in infants ≤28 days of age.
- When treating empirically, antibiotics that can be given by rapid IV bolus (eg, beta-lactam agents or cephalosporins) should be administered first, followed by infusions of antibiotics, such as vancomycin, that must be delivered more slowly.
- Ongoing antimicrobial therapy should be modified based upon culture results, including antimicrobial susceptibility and the patient's clinical course.

Examples of initial empiric antimicrobial regimens based upon patient age, level of immunocompetence, and previous antibiotic administration include:

- **Infants 0 to 28 days of age** (see "Management and outcome of sepsis in term and late preterm infants", section on 'Initial empiric therapy'):
  - Ampicillin (vancomycin in regions with a high prevalence of hospital-acquired MRSA)
  - **PLUS** ceftazidime or cefepime (cefotaxime, if available); meropenem if there is concern for infection due to a multidrug-resistant gram-negative organism
  - **PLUS** gentamicin
  - Add acyclovir for suspicion of HSV infection
- **Children >28 days of age who are normal hosts**:
  - Cefotaxime **or** ceftriaxone.
  - Add vancomycin if risk factors for MRSA are present. (See "Methicillin-resistant Staphylococcus aureus infections in children: Epidemiology and clinical spectrum", section on 'Epidemiology and risk factors'.)
  - For patients with a possible genitourinary source, add an aminoglycoside (eg, gentamicin).
  - For possible gastrointestinal source, add piperacillin with tazobactam, clindamycin, or metronidazole. It is best to avoid piperacillin-tazobactam if vancomycin is being administered because of the risk of renal injury when these two antibiotics are co-administered.
  - In the presence of septic shock in settings with resistant organisms or in at-risk patients, add combination therapy (using at least two antibiotics of different antimicrobial classes) aimed at covering resistant organisms [9,47].
- **Children >28 days who are immunosuppressed or at risk for infection with *Pseudomonas* species**:
  - Cefepime **or** carbapenem (eg, imipenem, meropenem) in settings where bacterial organisms with extended-spectrum

beta-lactamase (ESBL) resistance are prevalent or for patients who have been recently (within two weeks) treated with broad-spectrum antibiotics (eg, third-generation cephalosporin or fluoroquinolone).

- Add vancomycin if risk factors for MRSA are present. (See "Methicillin-resistant Staphylococcus aureus infections in children: Epidemiology and clinical spectrum", section on 'Epidemiology and risk factors'.)
- If concerned about resistance to cefepime/ceftazidime/carbapenem, add an aminoglycoside (eg, gentamicin, amikacin).

- **Children who cannot receive penicillin or who have recently received broad-spectrum antibiotics**:
  - Meropenem.
  - Add vancomycin if risk factors for MRSA are present.(See "Methicillin-resistant Staphylococcus aureus infections in children: Epidemiology and clinical spectrum", section on 'Epidemiology and risk factors'.)
  - Aztreonam **or** ciprofloxacin **PLUS** clindamycin may be used instead of meropenem.
- **Patients at increased risk of fungal infection (eg, identified fungal source, immunocompromised with persistent fever on broad-spectrum antibiotics)**:
  - Add liposomal amphotericin B or an echinocandin (eg, caspofungin, micafungin) to the antimicrobial regimen [48]. If candidemia is suspected, an echinocandin is the agent of choice.
- **Patients with risk factors for rickettsial infection (eg, travel to or reside in an endemic region)**:
  - Add a tetracycline antibiotic (eg, doxycycline) to the antimicrobial regimen.

For neonates with clinical features concerning for HSV infection who may receive acyclovir, viral cultures of vesicles (if present), cerebrospinal fluid and surface (mouth, nasopharynx, eye, and anus can be obtained from one swab ending with the anal swab), and polymerase chain reaction testing (from cerebrospinal fluid and blood) for HSV should be obtained whenever possible. Concerning clinical features include family members with HSV infection, respiratory collapse, elevated transaminases, thrombocytopenia, and/or abnormal cerebrospinal fluid suggestive of HSV infection (table 9). (See "Neonatal herpes simplex virus infection: Clinical features and diagnosis", section on 'Clinical manifestations'.)

Patients at risk for adrenal insufficiency

— Patients at risk for absolute adrenal insufficiency due to purpura fulminans, recent or chronic treatment with corticosteroids, hypothalamic or pituitary abnormalities, or other causes of congenital or acquired adrenal insufficiency should be treated with stress-dose hydrocortisone early in the course of resuscitation (IV hydrocortisone 50 to 100 mg/m^2/day or approximately 2 to 4 mg/kg/day, intermittent or continuous infusion, maximum dose 200 mg/day). (See "Treatment of adrenal insufficiency in children".)

Causes and diagnosis of adrenal insufficiency in children are discussed separately. (See "Diagnosis of adrenal insufficiency in children" and "Causes and clinical manifestations of primary adrenal insufficiency in children" and "Causes and clinical manifestations of central adrenal insufficiency in children".)

Patients with fluid-refractory shock

— Vasoactive agents are indicated in patients with fluid-refractory septic shock and are frequently necessary in the initial resuscitation of children with septic shock while hypovolemia is corrected [5]. The choice of agent is determined by whether the blood pressure is normal or hypotensive for age.

Indications for vasoactive agents

— For patients who continue to have evidence of abnormal perfusion after 40 to 60 mL/kg of crystalloid fluid resuscitation, we suggest initiation of vasoactive therapy (eg, continuous infusion of epinephrine (table 5 and table 6) or norepinephrine) (algorithm 1). Additional fluid resuscitation may be concurrently administered if physiologic improvement continues to occur following each fluid bolus without signs of fluid overload. (See 'Fluid resuscitation' above.)

Central venous access is preferred for vasoactive therapy. However, peripheral IV access or IO cannula is acceptable while central venous access is being obtained. Initial therapy with epinephrine is suggested if myocardial dysfunction is present on cardiac ultrasound or other modality. Otherwise, first-line therapy with either epinephrine or norepinephrine is acceptable.

The need for vasoactive medications should be identified and administration begun within the first 60 minutes of resuscitation [1,2]. Although meeting this goal is technically feasible based upon one observational study performed in a tertiary care pediatric institution [7], the feasibility of this goal outside of pediatric tertiary care institutions has not been studied.

Hypotensive patients

— For infants with fluid-refractory, hypotensive septic shock, we suggest vasoactive therapy with either an epinephrine infusion or norepinephrine infusion rather than a dopamine infusion (algorithm 1). The choice between epinephrine and norepinephrine is guided by preference of the clinician, patient physiology, and local system factors [1]. Typically, epinephrine is used in patients with signs of myocardial dysfunction, and norepinephrine is used in patients with signs of low systemic vascular resistance or vasodilation:

- Epinephrine – For an epinephrine infusion, the initial starting dose is 0.05 to 0.1 mcg/kg/minute; titrate to response up to 1.5 mcg/kg/minute [8]. Examples of how to prepare an epinephrine infusion for a 10-kg or 20-kg child are provided in the tables (table 5 and table 6). At doses exceeding 0.1 mcg/kg/minute (and possibly lower in some patients), alpha-adrenergic effects of epinephrine are more pronounced, and systemic vasoconstriction may be more evident. We typically add a second vasopressor

if patients have not responded to an epinephrine dose of 1.5 mcg/kg/minute.

- Norepinephrine – For a norepinephrine infusion, the initial dose starting dose is 0.05 to 0.1 mcg/kg/minute; titrate to desired effect up to 2 mcg/kg/minute. Norepinephrine (Levophed) acts on both alpha-1 and beta-1 adrenergic receptors, thus producing potent vasoconstriction as well as a modest increase in cardiac output. This physiologic effect counteracts the toxin-induced vasodilation frequently seen in patients with septic shock. Based upon one small observational study of children with septic shock, norepinephrine therapy is associated with improved cardiac index [49]. However, patients in this study frequently required additional vasoactive agents (eg, epinephrine) to maintain a normal cardiac index.

Vasoactive medication may be initially administered through peripheral venous or IO access if central venous access has not been established. However, central venous access should be obtained as soon as practical.

Further tailoring of the agent and dose can be made according to the type of septic shock as determined by advanced hemodynamic monitoring of the cardiac index and/or systemic vascular resistance. These can be quantified once invasive arterial blood pressure monitoring, ultrasound Doppler of the thoracic aorta, cardiac echocardiography, or $ScvO_2$ measurement is established [5,50]. (See "Septic shock in children: Ongoing management after resuscitation", section on 'Vasoactive drug therapy'.)

Previous guidelines recommended using bedside clinical signs to categorize septic shock in children as "warm" (presumably indicating high cardiac output and low systemic vascular resistance) or "cold" (presumably indicating low cardiac output and high systemic vascular resistance) [5]. However, the 2020 Surviving Sepsis Campaign pediatric guidelines suggest against using bedside clinical signs in isolation for this purpose and instead recommend use of advanced hemodynamic variables (eg, direct measures of cardiac output/cardiac index, systemic vascular resistance, and $ScvO_2$) in addition to physical examination to guide the ongoing resuscitation of children with septic shock or other sepsis-associated organ dysfunction. This change was based on a number of observational studies that demonstrated very poor correlation of bedside clinical signs with more direct measures of myocardial dysfunction, cardiac index, and systemic vascular resistance as measured by advanced monitoring [2,51].

Both epinephrine and norepinephrine are preferred over dopamine based on the results of two small, randomized controlled trials in children with fluid-refractory septic shock, which demonstrate improved survival with initiation and titration of epinephrine compared with dopamine [52,53]:

- In a single-center, blinded trial of 120 infants and children (1 month to 15 years of age) treated for fluid-refractory septic shock in a pediatric intensive care unit, patients who received infusions of dopamine rather than epinephrine had significantly higher mortality (21 versus 7 percent) and more health care-associated infections (29 versus 2 percent) [52]. In this study the dopamine titration was less potent than the epinephrine titration, which may, in part, explain the differences in outcome. This trial was also stopped early for potential harm.

- In another single-center, blinded trial of 60 infants and children (3 months to 12 years of age) with fluid-refractory septic shock who received dopamine at doses of 10 to 20 mcg/kg/minute or epinephrine 0.1 to 0.3 mcg/kg/minute, patients who received epinephrine were significantly more likely to have resolution of shock within the first hour than those who received dopamine (12 out of 29 versus 4 out of 31 patients; OR 4.8, 95% CI 1.3-17.2) [53]. Patients who received epinephrine also had significantly better organ function on day three of treatment and more organ failure-free days. Overall, mortality was similar in both groups.

Given the small size and limitations of these trials, a larger, multicenter trial that compares equipotent dosing of epinephrine with dopamine is necessary to confirm these findings [54].

There are no studies assessing norepinephrine in children with septic shock. Randomized trial in adults with septic shock demonstrate lower mortality rate in patients receiving norepinephrine compared with those receiving dopamine and similar mortality compared with those receiving epinephrine. (See "Evaluation and management of suspected sepsis and septic shock in adults", section on 'Vasopressors'.)

Normotensive patients

— Evidence is lacking to provide clear guidance for the management of infants and children with fluid-refractory shock and a normal blood pressure. We suggest that patients with persistent signs of shock but normal blood pressure after initial fluid resuscitation receive low-dose epinephrine infusions (eg, 0.03 to 0.05 mcg/kg/minute). These patients should also continue to receive fluid resuscitation unless signs of volume overload are present. If patients do not respond to fluid resuscitation augmented by low-dose epinephrine infusion, then vasodilatory agents (eg, dobutamine or milrinone) are typically employed. Close monitoring of clinical and laboratory parameters (ie, lactate, urine output, and heart rate) with frequent patient reassessment are necessary to guide the need for escalation of therapies [5].

Patients with catecholamine-resistant shock

— Patients with catecholamine-resistant shock warrant evaluation for unrecognized morbidities. Etiologies to evaluate during initial management include pneumothorax, pericardial effusion, intra-abdominal hypertension, ongoing blood loss, and overt adrenal insufficiency (see 'Patients at risk for adrenal insufficiency' above). Bedside ultrasound of the lungs, heart, and abdomen by a properly trained and experienced provider may supplement more definitive imaging [55]. (See "Septic shock in children: Ongoing management after resuscitation", section on 'Treat reversible etiologies'.)

We suggest that previously healthy patients who persist with shock in spite of rapid fluid administration and vasoactive infusion receive hydrocortisone in stress doses (50 to 100 mg/m^2/day or approximately 2 to 4 mg/kg/day, intermittent or continuous infusion, maximum dose 200 mg/day) (table 10) [5]. Such patients may have relative adrenal insufficiency, more recently termed "critical illness-related corticosteroid insufficiency." However, because definitive evidence of benefit in children is lacking, ongoing management without corticosteroid therapy is a reasonable alternative [1,2].

Evidence is also lacking regarding the best method to identify adrenal insufficiency in children with refractory septic shock or whether or not it is beneficial to assess adrenal status (either baseline serum cortisol or adrenocorticotropin hormone stimulation testing) prior to corticosteroid administration. Our typical approach is to consider treating with stress-dose hydrocortisone if patients remain in shock despite fluid resuscitation and initial vasoactive medication titration. (See "Septic shock in children: Ongoing management after resuscitation", section on 'Adrenal insufficiency'.)

In patients who require high-dose catecholamines, it is also reasonable to add vasopressin. However, because vasopressin has been associated with increased risk of ischemic events without a clear survival benefit, further titrating catecholamines in children with septic shock who require high-dose catecholamines is a reasonable alternative [1,2]. This decision should be made in consultation with a pediatric critical care specialist whenever possible. (See "Septic shock in children: Ongoing management after resuscitation", section on 'Vasoactive drug therapy'.)

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. Children with septic shock who present to facilities without the necessary clinical expertise or resources should undergo timely transfer to an appropriate facility. Use of a pediatric-specialized team is associated with improved patient survival and fewer adverse effects during transport. Thus, the use of pediatric-specialized teams for transport of children with septic shock is recommended whenever it is available. (See "Prehospital pediatrics and emergency medical services (EMS)", section on 'Inter-facility transport'.)

OUTCOMES

— Increased attention to rapid recognition, aggressive fluid administration, and early administration of vasoactive agents and antibiotics has been associated with a significant decrease in pediatric mortality from severe sepsis and septic shock [4,5,56-59]. With best clinical practices, mortality from septic shock in resource-rich settings is 0 to 5 percent among previously healthy children and 10 percent in chronically ill children. In one observational study, mortality was 19 percent among children who had persistent shock at pediatric intensive care unit admission, 62 percent of whom did not receive fluid administration and initiation of vasoactive infusions according to guidelines [60]. In another prospective observational study, mortality from septic shock was 1 percent among children who met goals for timely administration of fluids and antibiotics versus 4 percent for those who did not (adjusted odds of death 0.2, 95% CI 0.07-0.53) [16].

However, for critically ill children requiring admission to an intensive care unit who develop multiple organ dysfunction syndrome, mortality rates between 10 to 25 percent have been reported [61-63]. Notably, in a single-center study of 321 children treated for septic shock admitted to a pediatric intensive care unit, the administration of rapid IV fluids, antibiotics, and vasoactive infusions within the first hour of shock recognition was associated with a nonsignificant trend toward lower mortality (3.4 versus 6.4 percent) and less new or progressive multiple organ dysfunction syndrome (7.7 versus 12.3 percent) [17].

SOCIETY GUIDELINE LINKS

— Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Sepsis in children and adults" and "Society guideline links: Shock in children".)

SUMMARY AND RECOMMENDATIONS

Settings with pediatric intensive care

- Each pediatric institution should develop a multidisciplinary approach to early identification of septic shock with employment of a septic shock screening tool (algorithm 2) and timely clinical assessment and initiation of resuscitation in children with suspected septic shock. (See 'Institutional approach' above.)
- A clinical diagnosis of severe sepsis or septic shock is made in children who have signs of inadequate tissue perfusion, two or more criteria for the systemic inflammatory response syndrome (table 1), and suspected or proven infection. (See 'Rapid recognition' above and 'Red-flag findings' above and 'Signs and symptoms of infection' above.)
- Our approach to children with septic shock receiving care in facilities with access to intensive care, including advanced airway and circulatory support (algorithm 1), is largely consistent with the 2020 Surviving Sepsis Campaign guidelines provided by the initial resuscitation algorithm for children. Each pediatric institution should develop a multidisciplinary approach to the resuscitation of children with septic shock (ie, a resuscitation protocol/guideline) that codifies the time-limited stabilization tasks recommended within the first hour of treatment and mobilizes institutional resources such as electronic health record systems and quality improvement activities to meet those goals. (See 'Approach' above and 'Institutional guidelines and protocols' above.)
- Priorities for airway and breathing include (see 'Airway and breathing' above):
    - Patients with septic shock and hypoxemia should initially receive supplemental oxygen, as needed, to avoid hypoxemia. A trial of noninvasive ventilation, such as continuous positive airway pressure ventilation or bilevel positive airway pressure ventilation, may avoid the need for endotracheal intubation in selected patients. (See 'Airway and breathing' above.)
    - Endotracheal intubation using rapid sequence intubation (RSI) is frequently necessary in children with septic shock (table 3). Patients with hemodynamic instability should receive appropriate interventions to achieve hemodynamic stability as described below prior to or during intubation. When performing RSI in children with septic shock, ketamine, if available and **not** contraindicated (ie, patients younger than three months of age or with psychosis), is suggested for sedation prior

to endotracheal intubation. (See 'Airway and breathing' above.)

- Etomidate is not recommended unless ketamine is not available or is contraindicated by psychosis. Fentanyl in doses of 1 to 2 mcg/kg given slowly is suggested for infants younger than three months of age. (See 'Airway and breathing' above.)

- Key aspects of managing circulation during the first hour after recognition of septic shock include:

  - Intravenous (IV) access (preferably two sites and of the largest caliber that can be reliably inserted) should be established within five minutes of recognition of septic shock. If a peripheral IV cannot be started in this time, then intraosseous (IO) access should be obtained. Suggested laboratory studies for children with sepsis and septic shock as listed above should be drawn as vascular access is achieved. (See 'Obtain laboratory studies' above.)

  - Rapid blood glucose and serum ionized calcium should be measured as IV access is obtained. If present, hypoglycemia (table 4) or symptomatic hypocalcemia should be corrected. (See 'Treat hypoglycemia' above and 'Treat hypocalcemia' above.)

  - Children with septic shock and no signs of fluid overload should receive 10 to 20 mL/kg of balanced crystalloid solution (eg, lactated Ringer's solution) or normal saline. Fluid volume should be calculated based upon ideal body weight (eg, 50th percentile for age (figure 1A-B and figure 2A-B)). We suggest using balanced crystalloid fluids (eg, lactated Ringer's) for fluid resuscitation, although 0.9% saline remains an effective alternative (**Grade 2C**). Infusion of this amount of fluid over 5 to 10 minutes can be achieved with a manual "push-pull" technique or rapid infuser. (See 'Fluid resuscitation' above.)

  - If the patient develops signs of fluid overload (eg, rales, worsening respiratory distress, new or worsening oxygen requirement, gallop rhythm, hepatomegaly, or cardiomegaly or pulmonary edema on chest radiograph), the fluid bolus should be omitted or reduced (eg, 5 to 10 mL/kg given over 15 minutes) and continued septic shock treated with vasoactive infusions. Patients with signs of fluid overload who continue to receive fluid boluses warrant close monitoring for respiratory and cardiac failure. The clinician should have a low threshold for endotracheal intubation and mechanical ventilation to treat pulmonary edema in these patients. (See 'Fluid resuscitation' above.)

  - After the initial infusion, the patient should be quickly reassessed for signs of inadequate end-organ perfusion to determine if additional fluid is needed and to identify any signs of fluid overload (eg, pulmonary rales or gallop rhythm). (See 'Facilities with access to intensive care' above.)

  - For children who continue to have evidence of abnormal perfusion after 40 to 60 mL/kg of crystalloid fluid resuscitation, we suggest initiation of vasoactive therapy (eg, continuous infusion of epinephrine (table 5 and table 6) or norepinephrine). The choice of agent is determined by whether the blood pressure is normal or hypotensive for age (table 1):

    - For children with fluid-refractory, hypotensive septic shock, we suggest vasoactive therapy with either an epinephrine infusion or norepinephrine infusion rather than a dopamine infusion (**Grade 2C**).

    - For children with fluid-refractory, normotensive septic shock, we suggest vasoactive therapy with low-dose epinephrine infusion rather than norepinephrine or dopamine (**Grade 2C**).

  - Additional fluid resuscitation may be concurrently administered if physiologic improvement continues to occur following each fluid bolus and the patient has no signs of fluid overload.

- Antimicrobial therapy should be started within the first hour of resuscitation (see 'Timing' above). Effective delivery of broad-spectrum antibiotics usually requires two ports or sites for IV access: one devoted to fluid resuscitation and one for antimicrobial delivery. Antifungal and antiviral agents should be included as part of the initial regimen for susceptible patients. (See 'Empiric antibiotic therapy' above.)

- Patients at risk for absolute adrenal insufficiency should be treated with stress-dose hydrocortisone early in the course of resuscitation. (See 'Patients at risk for adrenal insufficiency' above.)

- Patients with catecholamine-resistant shock warrant evaluation for unrecognized morbidities such as pneumothorax, pericardial effusion, intra-abdominal hypertension, and ongoing blood loss. In addition, for previously healthy patients who persist with catecholamine-resistant shock in spite of rapid fluid administration and vasoactive infusion, we suggest stress-dose corticosteroid therapy (eg, IV hydrocortisone 50 to 100 mg/m^2/day or approximately 2 to 4 mg/kg/day, intermittent or continuous infusion, maximum dose 200 mg/day) (table 10) (**Grade 2C**). However, because definitive evidence of benefit in children is lacking, ongoing management without corticosteroid therapy is a reasonable alternative. (See 'Patients with catecholamine-resistant shock' above.)

- In patients with catecholamine-resistant shock, it is also reasonable to add vasopressin. However, because vasopressin has been associated with increased risk of ischemic events without a clear survival benefit, further titrating epinephrine and/or norepinephrine to higher doses in children with septic shock is a reasonable alternative.

- After initial resuscitation, ongoing aggressive management of septic shock should continue under the care of physicians with pediatric critical care expertise in a setting that has the necessary resources to provide pediatric intensive care. (See 'Transfer to definitive care' above and "Septic shock in children: Ongoing management after resuscitation".)

Resource-limited settings

- In resource-limited settings without access to intensive care with advanced airway and circulatory support, treatment of sepsis

or septic shock should be modified based on either hypotension or the World Health Organization (WHO) definition of shock as provided by the initial resuscitation algorithm for children (see 'Resource-limited settings' above):

- Severe sepsis – Patients with severe febrile illness, poor perfusion, and, if measured, normal blood pressure should receive maintenance fluids and **not** bolus fluid resuscitation.
- Septic shock – In patients with septic shock and hypotension, bolus fluids should be administered judiciously in aliquots of 10 to 20 mL/kg up to 40 mL/kg in the first hour. Fluid volume should be calculated based upon ideal body weight (eg, 50th percentile for age (figure 1A-B and figure 2A-B)). Fluid resuscitation should be titrated to cardiac output and discontinued if the patient develops clinical signs of fluid overload. We advise caution with both volume and speed of fluid boluses if access to mechanical ventilation is limited and life-threatening shock is not present.

- Patients with dehydration or ongoing fluid losses (eg, diarrhea or severe capillary leak as with dengue shock syndrome) should receive fluid therapy according to the WHO Emergency Triage Assessment and Treatment guidelines (table 7). (See "Dengue virus infection: Prevention and treatment", section on 'Management of plasma leakage'.)

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