SEPSIS

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2y rold with abscess rt foot is admitted with tachypnea ,tachycardia, flash crt is admitted with thrombocytopenia ,prolonged pt

Infection, documented or suspected, and some of the following:
General variables
Fever (> 38.3°C)
Hypothermia (core temperature < 36°C)
Heart rate > 90/min^{-1} or more than two SD above the normal value for age
Tachypnea
Altered mental status
Significant edema or positive fluid balance (> 20 mL/kg over 24 hr)
Hyperglycemia (plasma glucose > 140 mg/dL or 7.7 mmol/L) in the absence of diabetes
Inflammatory variables
Leukocytosis (WBC count > 12,000 μL^{-1})
Leukopenia (WBC count < 4000 μL^{-1})
Normal WBC count with greater than 10% immature forms
Plasma C-reactive protein more than two SD above the normal value
Plasma procalcitonin more than two SD above the normal value
Hemodynamic variables
Arterial hypotension (SBP < 90 mm Hg, MAP < 70 mm Hg, or an SBP decrease > 40 mm Hg in adults or less than two SD below normal for age)
Organ dysfunction variables
Arterial hypoxemia (Pao_2/Fio_2 < 300)
Acute oliguria (urine output < 0.5 mL/kg/hr for at least 2 hrs despite adequate fluid resuscitation)
Creatinine increase > 0.5 mg/dL or 44.2 μmol/L
Coagulation abnormalities (INR > 1.5 or aPTT > 60 s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count < 100,000 μL^{-1})
Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 μmol/L)
Tissue perfusion variables
Hyperlactatemia (> 1 mmol/L)
Decreased capillary refill or mottling

WBC = white blood cell; SBP = systolic blood pressure; MAP = mean arterial pressure; INR = international normalized ratio; aPTT = activated partial thromboplastin time.

Diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature > 38.5° or < 35°C), tachycardia (may be absent in hypothermic patients), and at least one of the following indications of altered organ function: altered mental status, hypoxemia, increased serum lactate level, or bounding pulses.

Adapted from Levy MM, Fink MP, Marshall JC, et al: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; 31: 1250–1256.

Severe sepsis definition = sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)
Sepsis-induced hypotension
Lactate above upper limits laboratory normal
Urine output < 0.5 mL/kg/hr for more than 2 hrs despite adequate fluid resuscitation
Acute lung injury with Pao_2/Fio_2 < 250 in the absence of pneumonia as infection source
Acute lung injury with Pao_2/Fio_2 < 200 in the presence of pneumonia as infection source
Creatinine > 2.0 mg/dL (176.8 μmol/L)
Bilirubin > 2 mg/dL (34.2 μmol/L)
Platelet count < 100,000 μL
Coagulopathy (international normalized ratio > 1.5)

Adapted from Levy MM, Fink MP, Marshall JC, et al: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; 31: 1250–1256.

SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:
1) Measure lactate level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad spectrum antibiotics
4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥4mmol/L

TO BE COMPLETED WITHIN 6 HOURS:
5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation ($Scvo_2$)*
7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, $Scvo_2$ of ≥70%, and normalization of lactate.

PEDIATRIC CONSIDERATIONS IN SEVERE SEPSIS

While sepsis in children is a major cause of death in industrialized countries with state-of-the-art ICUs, the overall mortality from severe sepsis is much lower than that in adults, estimated at about2% to 10% (497–499). The hospital mortality rate for severe sepsisis 2% in previously healthy children and 8% in chronically ill children in the United States (497). Definitions of sepsis, severe sepsis,septic shock, and multiple organ dysfunction/failure syndromesare similar to adult definitions but depend on age-specific heart rate, respiratory rate, and white blood cell count cutoff values(500, 501). This document provides recommendations only forterm newborns and children in the industrialized resource-rich setting with full access to mechanical ventilation ICUs**A.**

Initial Resuscitation

- We suggest starting with oxygen administered by face mask or, if needed and available, high-flow nasal cannula oxygen or nasopharyngeal continuous positive airway pressure (CPAP) for respiratory distress and hypoxemia. Peripheral intravenous access or intraosseous access can be used for fluid resuscitation and inotrope infusion when a central line is notavailable. If mechanical ventilation is required, then

cardiovascular instability during intubation is less likely after appropriatecardiovascular resuscitation (grade 2C).

- ***Rationale*.** Due to low functional residual capacity, younginfants and neonates with severe sepsis may require early intubation; however, during intubation and mechanical ventilation

Recommendations: Special Considerations in Pediatrics

A. Initial Resuscitation

1. For respiratory distress and hypoxemia start with face mask oxygen or if needed and available, high flow nasal cannula oxygen or nasopharyngeal CPAP (NP CPAP). For improved circulation, peripheral intravenous access or intraosseus access can be used for fluid resuscitation and inotrope infusion when a central line is not available. If mechanical ventilation is required then

cardiovascular instability during intubation is less likely after appropriate cardiovascular resuscitation (grade 2C).

2. Initial therapeutic end points of resuscitation of septic shock: capillary refill of ≤2 secs, normal blood pressure for age, normal pulses with no differential between peripheral and central pulses, warm extremities, urine output >1 $mL \cdot kg^{-1} \cdot hr^{-1}$, and normal mental status.Scv_{O2} saturation ≥70% and cardiac index between 3.3 and 6.0 $L/min/m^2$ should be targeted thereafter (grade 2C).

3. Follow American College of Critical Care Medicine-Pediatric Life Support (ACCM-PALS) guidelines for the management of septic shock (grade 1C).

4. Evaluate for and reverse pneumothorax, pericardial tamponade, or endocrine emergencies in patients with refractory shock (grade 1C).

B. Antibiotics and Source Control

1. Empiric antibiotics be administered within 1 hr of the identification of severe sepsis. Blood cultures should be obtained before administering antibiotics when possible but this should not delay administration of antibiotics. The empiric drug choice should be changed as epidemic and endemic ecologies dictate (eg H1N1, MRSA, chloroquine resistant malaria, penicillin-resistant
pneumococci, recent ICU stay, neutropenia) (grade 1D).
2. Clindamycin and anti-toxin therapies for toxic shock syndromes with refractory hypotension (grade 2D).
3. Early and aggressive source control (grade 1D).
4. *Clostridium difficile* colitis should be treated with enteral antibiotics if tolerated. Oral vancomycin is preferred for severe disease (grade 1A).

C. Fluid Resuscitation

1. In the industrialized world with access to inotropes and mechanical ventilation, initial resuscitation of hypovolemic shock begins with infusion of isotonic crystalloids or albumin with boluses of up to 20 mL/kg crystalloids (or albumin equivalent) over 5–10 minutes, titrated to reversing hypotension, increasing urine output, and attaining normal capillary refill, peripheral pulses, and level of consciousness without inducing hepatomegaly or rales. If hepatomegaly or rales exist then inotropic support should be implemented, not fluid resuscitation. In non-hypotensive children with severe hemolytic anemia (severe malaria or sickle cell
crises) blood transfusion is considered superior to crystalloid or albumin bolusing (grade 2C).

D. Inotropes/Vasopressors/Vasodilators

1. Begin peripheral inotropic support until central venous access can be attained in children who are not responsive to fluid resuscitation (grade 2C).
2. Patients with low cardiac output and elevated systemic vascular resistance states with normal blood pressure be given vasodilator therapies in addition to inotropes (grade 2C).

E. Extracorporeal Membrane Oxygenation (ECMO)

1. Consider ECMO for refractory pediatric septic shock and respiratory failure (grade 2C).

F. Corticosteroids

1. Timely hydrocortisone therapy in children with fluid refractory, catecholamine resistant shock and suspected or proven absolute (classic) adrenal insufficiency (grade 1A).

G. Protein C and Activated Protein Concentrate

No recommendation as no longer available.

H. Blood Products and Plasma Therapies
1. Similar hemoglobin targets in children as in adults. During resuscitation of low superior vena cava oxygen saturation shock (< 70%), hemoglobin levels of 10 g/dL are targeted. After stabilization and recovery from shock and hypoxemia then a lower target > 7.0 g/dL can be considered reasonable (grade 1B).
2. Similar platelet transfusion targets in children as in adults (grade 2C).
3. Use plasma therapies in children to correct sepsis-induced thrombotic purpura disorders, including progressive disseminated intravascular coagulation, secondary thrombotic microangiopathy, and thrombotic thrombocytopenic purpura (grade 2C).

I. Mechanical Ventilation.
1 Lung-protective strategies during mechanical ventilation (grade 2C)

Recommendations: Special Considerations in Pediatrics

J. Sedation/Analgesia/Drug Toxicities
1. We recommend use of sedation with a sedation goal in critically ill mechanically ventilated patients with sepsis (grade 1D).
2. Monitor drug toxicity labs because drug metabolism is reduced during severe sepsis, putting children at greater risk of adverse drug-related events (grade 1C).

K. Glycemic Control
1. Control hyperglycemia using a similar target as in adults ≤ 180 mg/dL. Glucose infusion should accompany insulin therapy in newborns and children because some hyperglycemic children make no insulin whereas others are insulin resistant (grade 2C).

L. Diuretics and Renal Replacement Therapy
1. Use diuretics to reverse fluid overload when shock has resolved, and if unsuccessful then continuous venovenous hemofiltration (CVVH) or intermittent dialysis to prevent > 10% total body weight fluid overload (grade 2C).

M. Deep Vein Thrombosis (DVT) Prophylaxis
No recommendation on the use of DVT prophylaxis in prepubertal children with severe sepsis.

N. Stress Ulcer(SU) Prophylaxis
No recommendation on the use of SU prophylaxis in prepubertal children with severe sepsis.
O. Nutrition
1. Enteral nutrition given to children who can be fed enterally, and parenteral feeding in those who cannot (grade 2C).

- increased intrathoracic pressure can reduce venous return and lead to worsening shock if the patient is not volume loaded. In those who desaturate despite administration of face mask oxygen, high-flow nasal cannula oxygen or nasopharyngeal CPAP can be used to increase functional residual capacity and reduce the work of breathing, allowing for establishment of intravenous or intraosseous access for fluid resuscitation and peripheral inotrope delivery (502, 503). Drugs used for sedation have important side effects in these patients. For example, etomidate is associated with increased mortality in children with meningococcal sepsis because of adrenal suppression effect (504, 505). Because attainment of central access is more difficult in children than adults, reliance on peripheral or intraosseous access can be substituted until and unless central access is available.
- 2. We suggest that the initial therapeutic endpoints of resuscitation of septic shock be capillary refill of ≤ 2 s, normal blood pressure for age, normal pulses with no differential between peripheral and central pulses, warm extremities, urine output > 1 mL/kg/hr, and normal mental status. Thereafter, Scv_{o_2}saturation greater than or equal to 70% and cardiac index between 3.3 and 6.0 L/min/m_2 should be targeted (grade 2C).
- ***Rationale.*** Adult guidelines recommend lactate clearance as well, but children commonly have normal lactate levels with septic shock. Because of the many modalities used to measure S_{cvo_2} and cardiac index, the specific choice is left to the practitioner's discretion (506–512).
- 3. We recommend following the American College of Critical Care Medicine-Pediatric Advanced Life Support guidelines for the management of septic shock (grade 1C). ***Rationale.*** The recommended guidelines are summarized in **Figure 2** (510–512).

- 4. We recommend evaluating for and reversing pneumothorax, pericardial tamponade, or endocrine emergencies in patients with refractory shock (grade 1C).
- ***Rationale.*** Endocrine emergencies include hypoadrenalism and hypothyroidism. In select patients, intra-abdominal hypertension may also need to be considered (513–515).

B. Antibiotics and Source Control

- We recommend that empiric antimicrobials be administered within 1 hr of the identification of severe sepsis. Blood cultures should be obtained before administering antibiotics when possible, but this should not delay initiation of antibiotics. The empiric drug choice should be changed as epidemic and endemic ecologies dictate (eg, H1N1, methicillin- resistant *S. aureus*, chloroquine-resistant malaria, penicillin-resistant pneumococci, recent ICU stay, neutropenia) (grade 1D).
- ***Rationale.*** Vascular access and blood drawing is more difficult in newborns and children. Antimicrobials can be given intramuscularly or orally (if tolerated) until intravenous line access is available (516–519).
- 2. We suggest the use of clindamycin and antitoxin therapies for toxic shock syndromes with refractory hypotension (grade 2D).
- ***Rationale.*** Children are more prone to toxic shock than adults because of their lack of circulating antibodies to toxins. Children with severe sepsis and erythroderma and suspected toxic shock should be

treated with clindamycin to reduce toxin production. The role of IVIG in toxic shock syndrome

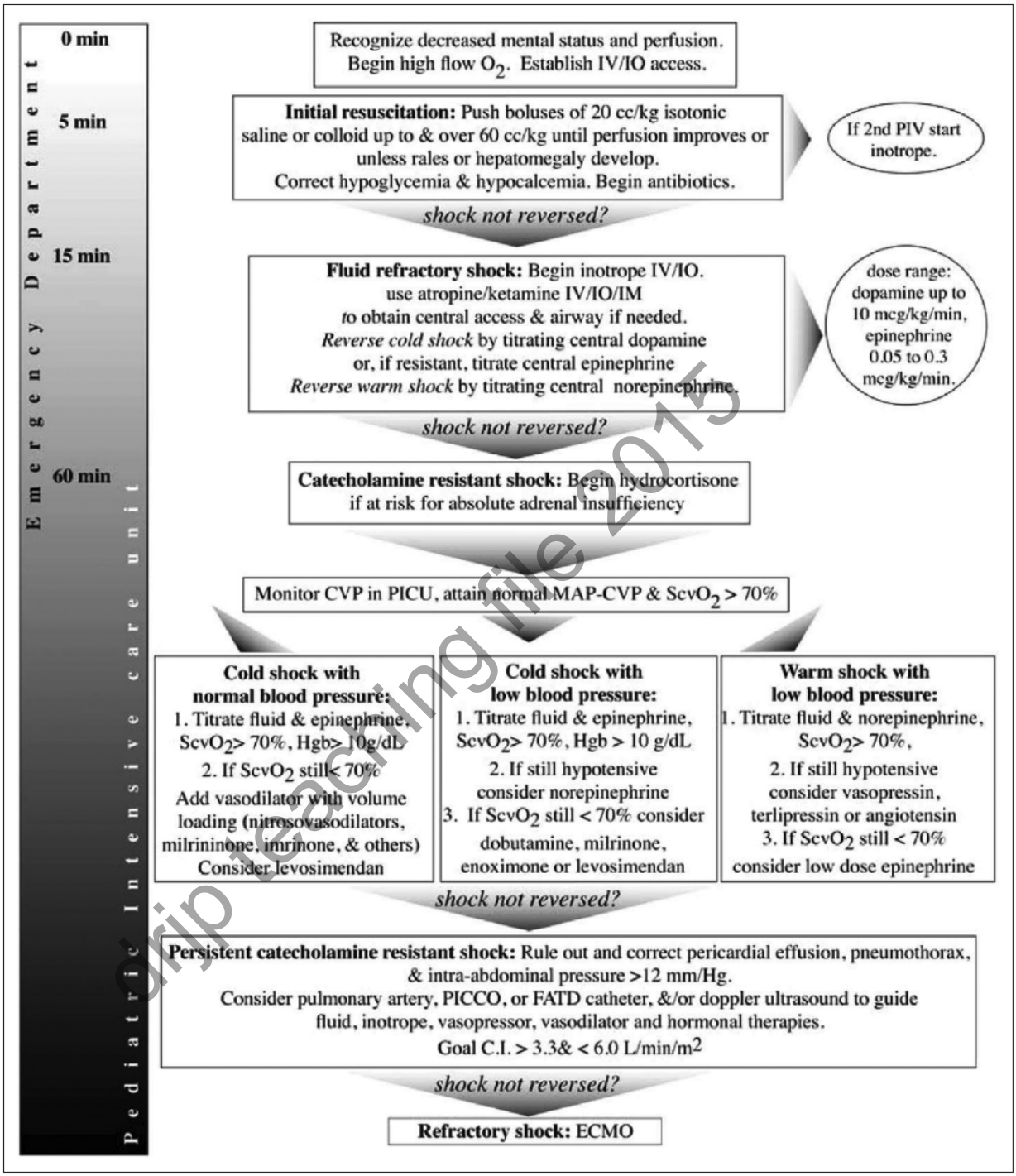

Figure 2. Algorithm for time sensitive, goal-directed stepwise management of hemodynamic support in infants and children. Reproduced from Brierley J, Carcillo J, Choong K, et al: Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. *Crit Care Med* 2009; 37:666–688.

is unclear, but it may be considered in refractory toxic shock syndrome (520–527).

- 3. We recommend early and aggressive infection source control (grade 1D)
- ***Rationale.*** Débridement and source control is paramount in severe sepsis and septic shock. Conditions requiring debridement or drainage include necrotizing pneumonia, necrotizing fasciitis,gangrenous myonecrosis, empyema, and abscesses. Perforatedviscus requires repair and peritoneal washout. Delay in

use of an appropriate antibiotic, inadequate source control, and failure to remove infected devices are associated with increased mortality in a synergistic manner (528–538).

- 4. *C. difficile* colitis should be treated with enteral antibiotics if tolerated. Oral vancomycin is preferred for severe disease (grade 1A).
- ***Rationale.*** In adults, metronidazole is a first choice; however, response to treatment with *C. difficile* can be best with enteral vancomycin. In very severe cases where diverting ileostomy or colectomy is performed, parenteral treatment should be considered until clinical improvement is ascertained (539–541).

C. Fluid Resuscitation

- In the industrialized world with access to inotropes and mechanical ventilation, we suggest that initial resuscitationof hypovolemic shock begin with infusion of isotoniccrystalloids or albumin, with boluses of up to 20 mL/kgfor crystalloids (or albumin equivalent) over 5 to 10 mins. These should be titrated to reversing hypotension, increasingurine output, and attaining normal capillary refill, peripheral pulses and level of consciousness without inducinghepatomegaly or rales. If hepatomegaly or rales develop,inotropic support should be implemented, not fluid resuscitation.In children with severe hemolytic anemia (severe malaria or sickle cell crises) who are not hypotensive, blood transfusion is considered superior to crystalloid or albumin bolusing (grade 2C).
- ***Rationale.*** Three RCTs compared the use of colloid to crystalloid resuscitation in children with hypovolemic dengue shock with near 100% survival in all treatment arms (542–544). In the industrialized world, two before-and-after studies observed 10-fold reductions in mortality when children with purpura/meningococcal septic shock were treated with fluid boluses, inotropes, and mechanical ventilation in the community emergency department (545, 546). In one randomized trial, septic shock mortality was reduced (40% to 12%) when increased fluid boluses, blood, and inotropes were given to attain a Scv_{O2} monitoring goal of greater than 70% (511). A quality improvement study achieved a reduction in severe sepsis mortality (from 4.0% to 2.4%) with the delivery of fluidboluses and antibiotics in the first hour in a pediatric emergency department to reverse clinical signs of shock (547).
- Children normally have a lower blood pressure than adults, and a fall in blood pressure can be prevented by vasoconstriction and increasing heart rate. Therefore, blood pressure alone is not a reliable endpoint for assessing the adequacy of resuscitation. However, once hypotension occurs, cardiovascular collapse may soon follow. Thus, fluid resuscitation is recommended for both normotensive and hypotensive children in hypovolemic shock (542–554). Because hepatomegaly and/or rales occur in children who are fluid overloaded, these findings can be helpful signs of hypervolemia. In the absence of these signs, large fluid deficits can exist, and initial volume resuscitation can require 40 to 60 mL/kg or more; however, if these signs are present, then fluid administration should be ceased and diuretics should be given. Inotrope infusions and mechanical ventilation are commonly required for children with fluid-refractory shock.

D. Inotropes/Vasopressors/Vasodilators

- We suggest beginning peripheral inotropic support untilcentral venous access can be attained in children who are not responsive to fluid resuscitation (grade 2C).
- ***Rationale.*** Cohort studies show that delay in the use of inotropic therapies is associated with major increases in mortality risk (553, 554). This delay is often related to difficulty in attaining central access. In the initial resuscitationphase, inotrope/vasopressor therapy may be required to sustainperfusion pressure, even when hypovolemia has not yetbeen resolved. Children with severe sepsis can present withlow cardiac output and high systemic vascular resistance,high cardiac output and low systemic vascular resistance,or low cardiac output and low systemic vascular resistanceshock (555). A child may move from one hemodynamicstate to another. Vasopressor or inotrope therapy should be used according to the hemodynamic state (555). Dopaminerefractory shock may reverse with epinephrine or norepinephrine infusion. In the case of extremely low systemic vascular resistance despite the use of norepinephrine, the use of vasopressin and terlipressin has been described in a number of case reports, yet evidence to support this in pediatric sepsis, as well as safety data, are still lacking. Indeed, two RCTs showed no benefit in outcome with use of vasopressin or terlipressin in children (556–559). Interestingly, while vasopressin levels are reduced in adults with septic shock, such levels seem to vary extensively in children. When vasopressors are used for refractory hypotension, the addition of inotropes is commonly needed to maintain adequate cardiac output (510, 511, 555).
- 2. We suggest that patients with low cardiac output and elevated systemic vascular resistance states with normal blood pressure be given vasodilator therapies in addition to inotropes (grade 2C).

- ***Rationale.*** The choice of vasoactive agent is initially determined by the clinical examination; however, for the child with invasive monitoring in place and demonstration of a persistent low cardiac output state with high systemic vascular resistance and normal blood pressure despite fluid resuscitation and inotropic support, vasodilator therapy can reverse shock. Type III phosphodiesterase inhibitors (amrinone, milrinone, enoximone) and the calcium sensitizer levosimendan can be helpful because they overcome receptor desensitization. Other important vasodilators include nitrosovasodilators, prostacyclin, and fenoldopam. In two RCTs, pentoxifylline reduced mortality from severe sepsis in newborns (510, 560–569).

E. Extracorporeal Membrane Oxygenation

- We suggest ECMO in children with refractory septic shock or with refractory respiratory failure associated with sepsis (grade 2C).
- ***Rationale.*** ECMO may be used to support children and neonates with septic shock or sepsis-associated respiratory failure (570, 571). The survival of septic patients supported with ECMO is 73% for newborns and 39% for older children, and is highest in those receiving venovenous ECMO (572). Forty-one percent of children with a diagnosis of sepsis requiring ECMO for respiratory failure survive to hospital discharge (573). Venoarterial ECMO is useful in children with refractory septic shock (574), with one center reporting 74% survival to hospital discharge using central cannulation via sternotomy (575). ECMO has been used successfully in critically ill H1N1 pediatric patients with refractory respiratory failure (576, 577).

F. Corticosteroids

- We suggest timely hydrocortisone therapy in children with fluid-refractory, catecholamine-resistant shock and suspected or proven absolute (classic) adrenal insufficiency (grade 1A).
- ***Rationale.*** Approximately 25% of children with septic shock have absolute adrenal insufficiency. Patients at risk for absolute adrenal insufficiency include children with severe septic shock and purpura, those who have previously received steroid therapies for chronic illness, and children with pituitary or adrenal abnormalities. Initial treatment is hydrocortisone infusion given at stress doses (50 mg/m_2/24 hr); however, infusions up to 50 mg/kg/d may be required to reverse shock in the short-term. Death from absolute adrenal insufficiency and septic shock occurs within 8 hrs of presentation. Obtaining a serum cortisol level at the time empiric hydrocortisone is administered may be helpful (578–583).

G. Protein C and Activated Protein Concentrate

- See section, History of Recommendations Regarding Use of Recombinant Activated Protein C.

H. Blood Products and Plasma Therapies

- We suggest similar hemoglobin targets in children as in adults. During resuscitation of low superior vena cava oxygen saturation shock (< 70%), hemoglobin levels of 10 g/ dL are targeted. After stabilization and recovery from shock and hypoxemia, then a lower target > 7.0 g/dL can be considered reasonable (grade 1B).
- ***Rationale.*** The optimal hemoglobin for a critically ill child with severe sepsis is not known. A recent multicenter trial reported no difference in mortality in hemodynamically stable critically ill children managed with a transfusion threshold of 7 g/ dL compared with those managed with a transfusion threshold of 9.5 g/dL; however, the severe sepsis subgroup had an increase in nosocomial sepsis and lacked clear evidence of equivalence in outcomes with the restrictive strategy (584, 585). Blood transfusion is recommended by the World Health Organization for severe anemia, hemoglobin value < 5 g/dL, and acidosis. An RCT of early goal-directed therapy for pediatric septic shock using the threshold hemoglobin of 10 g/dL for patients with a Svc_{o_2} saturation less than 70% in the first 72 hrs of pediatric ICU admission showed improved survival in the multimodal intervention arm (511). 2. We suggest similar platelet transfusion targets in children as in adults (grade 2C).3. We suggest the use of plasma therapies in children to correct sepsis-induced thrombotic purpura disorders, including progressive disseminated intravascular coagulation, secondary thrombotic microangiopathy, and thrombotic thrombocytopenic purpura (grade 2C).
- ***Rationale.*** We give plasma to reverse thrombotic microangiopathies in children with thrombocytopenia-associated multiple organ failure and progressive purpura because fresh frozen plasma contains protein C, antithrombin III, and other anticoagulant proteins. Rapid resuscitation of shock reverses most disseminated intravascular coagulation; however, purpura progresses in some children in part due to critical consumption of antithrombotic proteins (eg, protein C, antithrombin III, ADAMTS 13). Plasma is infused with the goal

of correcting prolonged prothrombin/partial thromboplastin times and halting purpura. Large volumes of plasma require concomitant use of diuretics, continuous renal replacement therapy, or plasma exchange to prevent greater than 10% fluid overload (586–611).

I. Mechanical Ventilation

- We suggest providing lung-protective strategies during mechanical ventilation (grade 2C). ***Rationale.*** Some patients with ARDS will require increased PEEP to attain functional residual capacity and maintain oxygenation, and peak pressures above 30 to 35 cm H_2O to attain effective tidal volumes of 6 to 8 mL/kg with adequate CO_2 removal. In these patients, physicians generally transition from conventional pressure control ventilation to pressure release ventilation (airway pressure release ventilation) or to high-frequencyoscillatory ventilation. These modes maintain oxygenation with higher mean airway pressures using an "open" lung ventilation strategy. To be effective, these modes can require a mean airway pressure 5 cm H_2O higher than that used with conventional ventilation. This can reduce venous return leading to greater need for fluid resuscitation and vasopressor requirements (612–616).

J. Sedation/Analgesia/Drug Toxicities

- We recommend use of sedation with a sedation goal in critically ill mechanically ventilated patients with sepsis (grade 1D).
- ***Rationale.*** Although there are no data supporting any particular drugs or regimens, propofol should not be used for long-term sedation in children younger than 3 years because of the reported association with fatal metabolic acidosis. The use of etomidate and/or dexmedetomidine during septic shock should be discouraged, or at least considered carefully, because these drugs inhibit the adrenal axis and the sympathetic nervous system, respectively, both of which are needed for hemodynamic stability (617–620).2. We recommend monitoring drug toxicity labs because drug metabolism is reduced during severe sepsis, putting children at greater risk of adverse drug-related events (grade 1C).
- ***Rationale.*** Children with severe sepsis have reduced drug metabolism (621).

K. Glycemic Control

- We suggest controlling hyperglycemia using a similar target as in adults (≤ 180 mg/dL). Glucose infusion should accompany insulin therapy in newborns and children (grade 2C).
- ***Rationale.*** In general, infants are at risk for developing hypoglycemia when they depend on intravenous fluids. This means that a glucose intake of 4 to 6 mg/kg/min or maintenance fluid intake with dextrose 10% normal saline containing solution is advised (6−8 mg/kg/min in newborns). Associations have been reported between hyperglycemia and an increased risk of death and longer length of stay. A retrospective pediatric ICU study reported associations of hyperglycemia, hypoglycemia, and glucose variability with increased length of stay and mortality rates. An RCT of strict glycemic control compared to moderate control using insulin in a pediatric ICU population found a reduction in mortality with an increase in hypoglycemia. Insulin therapy should only be conducted with frequent glucose monitoring in viewof the risks for hypoglycemia which can be greater in newborns and children due to a) relative lack of glycogen stores and muscle mass for gluconeogenesis, and b) the heterogeneity of the population with some excreting no endogenous insulin and others demonstrating high insulin levels and insulin resistance (622–628).

L. Diuretics and Renal Replacement Therapy

- We suggest the use of diuretics to reverse fluid overload when shock has resolved and if unsuccessful, then continuous venovenous hemofiltration or intermittent dialysis to prevent greater than 10% total body weight fluid overload (grade 2C).
- ***Rationale.*** A retrospective study of children with meningococcemia showed an associated mortality risk when children received too little or too much fluid resuscitation (549, 553). A retrospective study of 113 critically ill children with multiple organ dysfunction syndrome reported that patients with less fluid overload before continuous venovenous hemofiltration had better survival (629–631),

M. DVT Prophylaxis

- We make no graded recommendations on the use of DVT prophylaxis in prepubertal children with severe sepsis.
- ***Rationale.*** Most DVTs in young children are associated with central venous catheters. Heparin-bonded catheters may decrease the risk of catheter-associated DVT. No data exist on the efficacy of UFH or LMWH prophylaxis to prevent catheterrelated DVT in children in the ICU (632, 633).

N. Stress Ulcer Prophylaxis

- We make no graded recommendations on stress ulcer prophylaxis.
- ***Rationale.*** Studies have shown that clinically important GI bleeding in children occurs at rates similar to those of adults. Stress ulcer prophylaxis is commonly used in children who are mechanically ventilated, usually with H_2 blockers or proton pump inhibitors, although its effect is not known (634, 635).

O. Nutrition

- Enteral nutrition should be used in children who can tolerate it, parenteral feeding in those who cannot (grade 2C).
- ***Rationale.*** Dextrose 10% (always with sodium-containing solution in children) at maintenance rate provides the glucose delivery requirements for newborns and children (636). Patients with sepsis have increased glucose delivery needs which can be met by this regimen. Specific measurement of caloric requirements are thought to be best attained using a metabolic cart as they are generally less in the critically ill child than in the healthy child.

Table 1. Comparing ISTH and TCH Criteria for DIC

Coagulation Test and ISTH Criteria	Score	TCH Values[a]
Platelet count, /μL		
>100,000	0	Sequential measurement
50,000–100,000	1	
<50,000	2	
Prolongation of PT, s		
<3	0	<2.6
3–6	1	2.6–5.6
>6	2	>5.6
Fibrinogen, mg/dL		
≥100	0	Sequential measurement
<100	1	
D-dimer, μg/mL FEU		
No increase	0	<1.5
Moderate increase	2	1.5–3.9

Strong increase	3	≥4
Interpretation		
Overt DIC	≥5	Overt DIC[b]

DIC, disseminated intravascular coagulation; FEU, fibrinogen equivalent unit; ISTH, International Society on Thrombosis and Haemostasis; PT, prothrombin time; TCH, Texas Children's Hospital.

L