Texas Children's Hospital

TEXAS CHILDREN'S HOSPITAL
EVIDENCE-BASED OUTCOMES CENTER
RECOGNITION AND INITIAL MANAGEMENT OF SEPTIC SHOCK
Evidence-Based Guideline

Definition: Shock is a complex clinical syndrome caused by an acute failure of circulatory function, with inadequate tissue and organ perfusion, where delivery of oxygen and substrates to body tissues, as well as removal of metabolic waste products are insufficient. [(1)] Sepsis is defined as abnormal temperature or leukocyte count, in addition to other abnormal vital signs, in the presence of proven or known invasive infection. Severe sepsis is defined as sepsis in combination with either cardiovascular organ dysfunction or acute respiratory distress. This condition may also exist when sepsis is combined with two or more other organ dysfunctions, including neurologic, renal, hepatic or hematologic systems. In children, septic shock is defined as proven or suspected infection with the presence of tachycardia and poor perfusion with or without hypotension. [(2)]

Epidemiology: Nationally, there are over 75,000 hospitalizations for severe sepsis per year. The incidence is highest in newborns and falls dramatically in older children. [(3)] The risk of death increases with increasing numbers of failing organs, from 7% for those with single-organ system failure to 53.1% for those with four organ systems or more failing. [(4)] In 2013, an estimated 1860 patients were treated at Texas Children's Hospital with septic shock. [(5)]

Etiology: The presumed most common causes of septic shock are of bacterial origin; however, any organism can precipitate septic shock, including bacteria, viruses, and fungi, especially in the immunocompromised patient. [(1)] In 2012, the most common pathogens identified in a cohort of previously healthy patients at Texas Children's Hospital (TCH) in septic shock were *Staphylococcus aureus, Streptococcus pneumoniae* and *group B streptococcus.* During the same time period, the most common pathogens identified in a cohort of children at TCH with co-morbidities and central venous lines included: *Staphylococcus aureus, Pseudomonas, and Enterobacter.* [(6)]

Inclusion Criteria:
All pediatric patients greater than 28 days old with a temperature abnormality and/or concern for infection **AND** who meet one of the following criteria:
- Three or more of the identified signs and symptoms of shock (Table 3) and/or abnormal vital signs (Table 2)
- High risk patient (Table 1) **AND** two or more of the identified signs and symptoms of shock (Table 3) and/or abnormal vital signs (Table 2)
- Hypotension (refer to Table 2)

Table 1. High Risk Conditions

Malignancy
Sickle Cell Disease and other patients with asplenia
Bone marrow transplant
Central or indwelling line/catheter
Solid organ transplant
Severe mental retardation/cerebral palsy
Immunodeficiency, immunocompromised or immunosuppression
Urogenital abnormalities (i.e. spina bifida)

Table 2. PALS Adjusted Vital Signs for Septic Shock [(7,8)]

Age	Heart Rate	Resp Rate	Systolic BP	Temp (°C)
0d - 1m	> 205	> 60	< 60	<36 or >38
> 1m - 3m	> 205	> 60	< 70	<36 or >38
> 3m - 1y	> 190	> 60	< 70	<36 or >38.5
> 1y - 2y	> 190	> 40	< 70 + (age in yr x 2)	<36 or >38.5
> 2y - 4y	> 140	> 40	< 70 + (age in yr x 2)	<36 or >38.5
> 4y - 6y	> 140	> 34	< 70 + (age in yr x 2)	<36 or >38.5
> 6y - 10y	> 140	> 30	< 70 + (age in yr x 2)	<36 or >38.5
> 10y - 13y	> 100	> 30	< 90	<36 or >38.5
> 13y	> 100	> 20	< 90	<36 or >38.5

Table 3. Signs and Symptoms of Shock [(2,9)]

	Sign and/or Symptom
Peripheral Pulses	Decreased or weak Bounding
Capillary refill	≥ 3 sec Flash (< 1 sec)
Skin	Mottled, cool Flushed, ruddy, erythroderma (other than face) Petechiae below the nipple, any purpura
Mental status	Decreased, irritability, confusion inappropriate crying or drowsiness, poor interaction with parents, lethargy, diminished arousability, obtunded

*↑ HR followed by ↓ HR with BP changes will be noted as shock becomes uncompensated.

Exclusion Criteria:
- Trauma
- Neonates (0-28 days old)
- Pregnancy
- Age > 18 years

Differential Diagnosis:
- Anaphylaxis
- Hypovolemia
- Urinary tract infection
- Fever without localizing symptoms
- Central line associated blood stream infection
- Congestive Heart Failure
- Neurogenic shock
- Sepsis
- Pneumonia
- Meningitis

Septic Shock in Neonates [10,11]

The signs of septic shock in the neonate are non-specific including respiratory distress, poor perfusion, tachycardia, temperature instability, inadequate feeding, poor tone, pale color, and tachypnea. Differential diagnoses for the newborn with suspected septic shock includes disseminated bacterial, viral, or fungal infection, congenital heart disease (CHD), inborn errors of metabolism, and perinatal asphyxia. If the neonate has fever, CSF pleocytosis, and is ill appearing, congenital viral infection such as Herpes Simplex Virus (HSV) should be considered in the differential diagnosis and testing for HSV should be sent from blood and CSF. Risk factors such as maternal history of chorioamnionitis, prolonged rupture of membranes, or maternal HSV infection at the time of delivery should be taken into consideration in the evaluation process.

If the patient is admitted from home and presenting with signs of CHD related septic shock, initial evaluation should occur in the CVICU. An echocardiogram can be a vital diagnostic tool in delineating the underlying cause of septic shock in infants presenting with signs of shock. Vascular access should be established and dextrose containing maintenance IV fluids should be given while evaluation is in progress. An umbilical venous catheter is the preferred vascular access in neonates with suspected septic shock within the first week of life if the umbilical vein is patent and viable. If the patient is hypovolemic, treatment should be initiated with crystalloid fluid boluses of 10 ml/kg. Low dose dopamine (5 mcg/kg/min) or epinephrine should be started and titrated as necessary to optimize perfusion. Packed red blood cells can be administered for treatment of anemia. If the patient is presenting from home, empiric antibiotic treatment can be initiated with antibiotics tailored based on age at presentation (early onset sepsis versus late onset sepsis). Previously hospitalized neonates with suspected septic shock should be empirically treated with antibiotics as specified in Baylor College of Medicine (BCM) guidelines. If suspecting meningitis, using a third generation cephalosporin can be considered for providing adequate CSF penetration. If suspected HSV infection, consider empiric treatment with acyclovir, especially in the setting of pneumonitis, hepatitis, coagulopathy, hypoglycemia, or vesicles.

Diagnostic Evaluation: A brief history and physical examination should be conducted concurrently with the prompt initiation of treatment.

History: Assess for

- Temperature instability
- Poor feeding
- Changes in mental status
- Difficulty breathing
- Decreased urine output
- Comorbid conditions

Physical Examination: [1,9,10]

The severity of the inflammatory response associated with septic shock increases over a continuum. Early signs and symptoms of septic shock are a result of the body's compensatory mechanisms while late signs are indicative of decompensation. Assess for the early indications of shock along with the signs below:

- Widened pulse pressure due to decreased diastolic pressures
- Normal systolic blood pressure

As the body begins to decompensate and organ dysfunction progresses, the late signs of shock be assessed. The patient may also exhibit: [1,9]

- Rapid shallow breathing
- Decreased respiratory rate
- Oliguria
- Cyanosis
- Hypotension

Continuously monitor:

- Heart rate and rhythm
- Oxygen saturation
- Blood pressure

Frequently Monitor:

- Temperature
- Urine output

Laboratory Tests: There is no single laboratory test that reliably predicts or confirms a patient's initial condition. Blood cultures are an essential part of the evaluation of septic shock. A trend in procalcitonin or lactate levels may be helpful when incorporated with clinical judgment.

Lab Test	Required	Consider
Blood culture	X	
Complete blood count (CBC) with platelet and differential	X	
Blood gas with Metabolites	X	
Chem 10 panel	X	
Procalcitonin		X
Lactate		X

Critical Points of Evidence

Evidence Supports

- Abnormal vital signs and indications of poor perfusion are the signs and/or symptoms that most reliably predict or confirm septic shock. [8,12-15] - Strong recommendation with low quality evidence

- Implement methods for early recognition of shock by non-physicians in order to improve outcomes. [8,16-18] - Strong recommendation with low quality evidence

- Initiate treatment consistent with PALS guideline prior to ED arrival for patients with suspected septic shock. [14] - Strong recommendation with low quality evidence

- Three boluses of 20 mL/kg of crystalloid fluid should be administered intravenously via push-pull, rapid infuser, or pressure bag with the first bolus given within 20 minutes of recognition of septic shock. *Adjust fluid volume and rapidity of administration for patients whose pre-existing condition precludes rapid, large volume fluid resuscitation. [14,19-29] - Strong recommendation with moderate quality evidence
  Remarks – There is an ongoing prospective randomized trial in progress comparing the effectiveness of lactated Ringer's versus normal saline for initial resuscitation in children with suspected sepsis. The content expert team will await results from this trial to determine if revisions should be made to this recommendation.

- Epinephrine (0.05 mcg/kg/min) or norepinephrine (starting dose: 0.05 mcg/kg/min) should be started in patients with fluid refractory shock. Vasopressor treatment should be tailored based on the patient's hemodynamic state. [30-37] – Strong recommendation with low quality evidence
  Remarks
  - Evidence supports starting with at least the minimum dose listed above. These medications may be titrated up to achieve the desired effect up to a maximum of:
    - Epinephrine **MAX** 1 mcg/kg/min
    - Norepinephrine **MAX** 2 mcg/kg/min

- Patients with malignancies, asplenics, a history of bone marrow transplant, central or indwelling lines/catheters, history of solid organ transplant, severe mental retardation and/or cerebral palsy, immunodeficiency, immunocompromise, or immunosuppression, and/or urogenital abnormalities have an increased risk of septic shock. [4,8,14,25-26,38] - Strong recommendation with low quality evidence

- Administer vancomycin and ceftriaxone as empiric antibiotics to previously healthy patients with suspected septic shock (including children with sickle cell disease or suspicion of meningitis). Nafcillin should be added for suspected Staphylococcus infections. [3,6,13,39-40] - Strong recommendation with moderate quality evidence

- Administer vancomycin and cefepime as empiric antibiotic treatment for immunocompromised and other high risk patients with suspected septic shock (excluding children with asplenia or sickle cell disease). Gentamicin should be added to the empiric treatment regimen for the subset of patients within this group that are unstable. In patients with a recent history (past 3 to 6 months) of multidrug-resistant organisms, consult the Infectious Disease service and consider adding a carbapenem empirically. [6,41-44] - Strong recommendation with moderate quality evidence

- Consider administration of stress-dose steroids for patients with catecholamine resistant shock. Consider obtaining a random cortisol level prior to administration of steroids, when feasible. [45-49] - Weak recommendation with very low quality evidence

- Consider treatment for anemia in patients with suspected septic shock. [50] – Weak recommendation with very low quality evidence

Evidence Lacking/Inconclusive

- Alternative methods for fluid delivery should be pursued, including intraosseous access, if rapid intravenous access is not obtained in a timely fashion in order to provide the first fluid bolus within 20 minutes of the recognition of septic shock. – Consensus recommendation

- Oxygen should be titrated to keep oxygen saturations within the patient's normal range. – Consensus recommendation

Evidence Against

- Single laboratory tests should not be used to inform about a patient's initial condition. [51-62] – Strong recommendation with low quality evidence

- Prediction models should not be applied during the initial management of patients with septic shock to identify patients at risk for multiple organ failure. [63-65] – Strong recommendation with low quality evidence

Condition-Specific Elements of Clinical Management

Treatment Recommendations:

Phase 1 – **Within five (5) minutes** from recognition of septic shock initiate the following:

- Cardiac monitors and continuous pulse oximetry
- Vital signs every 15 minutes
- Neuro vital signs every 30 minutes
- Administer supplemental oxygen therapy and/or respiratory support to keep oxygen saturations within patient's normal range.
- Strict intake and output

Phase 2 – **Within twenty (20) minutes** from recognition of septic shock initiate the following:

- Establish peripheral IV. If IV unattainable, start IO access.
- Draw labs on IV placement
- Completion of first fluid bolus of 20 mL/kg of crystalloid fluid intravenously (Table 4)
- Reassess for need of additional fluid resuscitation
- Consider inserting a foley catheter

Phase 3 – **Within sixty (60) minutes** from recognition of septic shock initiate the following:

- Administer antibiotics (Table 5)
- Establish second PIV (or IO if PIV cannot be established) and consider central line if not done.
- Consider 2nd and 3rd bolus of 20 mL/kg NS or colloid fluid up to and over 60 mL/kg until perfusion improves or unless rales or hepatomegaly develops (Table 4)
- Correct hypoglycemia and/or hypocalcemia, if necessary
- Consider treatment for anemia
- If patient on chronic steroids, give stress dose for adrenal insufficiency.
- Reassess for need of additional fluid resuscitation

Phase 4 – **Fluid Refractory Shock**

- Transfer to the ICU
- Evaluate hemodynamic state
- Reverse fluid refractory shock by titrating epinephrine (dose range: 0.05 to a MAX of 1 mcg/kg/min) or norepinephrine (dose range: 0.05 to a MAX of 2 mcg/kg/min).
- Obtain central access if it does not delay admission to ICU. Initiate venous saturation and central venous pressure monitoring.
- Reassess for need of additional fluid resuscitation

Phase 5 – **Catecholamine Resistant Shock**

- Administer hydrocortisone at a dose of 2 mg/kg (Table 7)
- When feasible, send a random cortisol level prior to steroid administration to help guide treatment once stabilized.
- If patient is resistant to fluids and catecholamines, then look for other causes of shock including:
    - Pericardial effusion
    - Tension pneumothorax
    - Abdominal compartment syndrome
    - Ongoing blood loss
    - Necrotic tissue
    - Inadequate source control infection
- Consider ECMO if prior interventions are not effective

Therapeutic End Points

Treatment for septic shock should be aimed at achieving the end points below:

- Normal mental status
- Age-appropriate vital signs (HR, RR, blood pressure)
- Capillary refill <3 secs
- Palpable distal pulses without a differential from central pulses
- Urine output >1 mL/kg/hr
- Warm extremities
- Normal glucose and ionized calcium concentration
- Mixed venous oxygen saturation >70%

Measures:

Outcomes-

- Mortality rate

Process-

- Number of times best practice alert (BPA) triggered and not shock patient
- Utilization of the shock order sets all phases
- Utilization of other order sets as defined in BPA
- Percentage of patients administered fluids within 20 min of recognition of shock
- Time to antibiotic administration after recognitions of shock
- Number of patients admitted and shock recognized after admission to inpatient unit within 12 hours
- Appropriate antibiotics administered (high risk vs. low risk)

Table 4. Bolus [66]

Bolus 1 - Within 20 min of identification of shock then reassess need for additional fluids up to 3 boluses	
Sodium CHLORide 0.9% (NS)	**Route: IV** 20 mL/kg Push/pull or rapid infuser
Patients whose condition prohibits rapid fluid resuscitation Sodium CHLORide 0.9% (NS)	**Route: IV** 10 mL/kg Push/pull or rapid infuser

Table 5. Antibiotics [66]

***Antibiotic Therapy* - Previously Healthy**	
Ceftriaxone	**Route: IV** 50 mg/kg MAX: 2000 mg/dose
Vancomycin	**Route: IV** 15 mg/kg MAX: 1500 mg/dose
Add for suspected Staph Infection Nafcillin	**Route: IV** 50 mg/kg MAX: 2000 mg/dose
Add for suspected intra-abdominal infection Piperacillin/tazobactam (Zosyn) and discontinue ceftriaxone and vancomycin	**Route: IV** 100 mg/kg MAX: 3000 mg/dose
***Antibiotic Therapy* - Sickle Cell Disease or other asplenia**	
Ceftriaxone	**Route: IV** 50 mg/kg MAX: 2000 mg/dose
Vancomycin	**Route: IV** 15 mg/kg MAX: 1500 mg/dose
Add for suspected Staph Infection Nafcillin	**Route: IV** 50 mg/kg MAX: 2000 mg/dose
Add for suspected intra-abdominal infection Piperacillin/tazobactam (Zosyn)	**Route: IV** 100 mg/kg MAX: 3000 mg/dose
***Antibiotic Therapy* - Immunocompromised and/or High Risk**	
Cefepime	**Route: IV** 50 mg/kg MAX: 2000 mg
Vancomycin	**Route: IV** 15 mg/kg MAX: 1500 mg/dose
Unstable patients Gentamicin	**Route: IV** 2.5 mg/kg MAX: 120 mg/dose
Suspected intra-abdominal process Metronidazole	**Route: IV** 7.5 mg/kg MAX: 500 mg

Table 6. Pressors[66]

Tailor vasopressor treatment based on hemodynamic state:	
EPINEPHrine	**Route: Continuous IV infusion** 0.05 mcg/kg/min Titrate to a MAX of 1 mcg/kg/min
Norepinephrine	**Route: Continuous IV infusion** 0.05 mcg/kg/min Titrate to a MAX of 2 mcg/kg/min

Table 7. Steroids[66]

Catecholamine Resistant Shock	
Hydrocortisone sodium succinate	**Route: IV** 2 mg/kg MAX dose: 200 mg

TCH Evidence-Based Outcomes Center
Clinical Algorithm for Septic Shock

0 - minute mark

Time of arrival or recognition

Recognize abnormal vital signs and altered mental status and perfusion^

No → OFF algorithm
Manage as appropriate to clinical findings

Yes

5 – minute mark

Within 5 min of arrival or recognition:
- Administer supplemental oxygen and/or respiratory support to keep oxygen saturation in normal range
- Insert PIV. If IV unattainable, establish IO access.
- Place on cardiac monitor and continuous pulse oximeter
- Vital signs every 15 min.
- Neuro checks every 30 min.
- Strict I & O's

^Inclusion Criteria:
All patients greater than 28 days old with a temperature abnormality and/or concern for infection **AND** who meet one of the following criteria:
- Three or more of the identified signs and symptoms of shock and/or abnormal vitals signs
- High risk patient **AND** two or more of the identified signs and symptoms of shock and/or abnormal vital signs
- Hypotension

20 – minute mark

Initial Resuscitation
Within 20 min. of arrival or recognition:
- Administer 1st bolus* of 20 mL/kg normal saline (NS) via push-pull, rapid infuser or pressure bag within 20 minutes
- Reassess need for additional fluid resuscitation
- Draw labs
- **Begin antibiotics within 60 minutes**
- Consider inserting a foley catheter

*Adjust fluid volume and speed of administration for patients whose pre-existing condition precludes rapid large volume fluid resuscitation

Clinical improvement

Yes → OFF algorithm
Manage as appropriate to clinical findings

No

#Vasopressor Concentrations for Peripheral / Central Access
Peripheral IV – safety of peripheral infusion based upon drug concentration not drug dose. All vasoactive agents can be given safely through an intraosseous line if there is no central access.
-Epinephrine: 0.01 mg/mL, 0.05 mg/mL, 0.2 mg/mL
-Norepinephrine: Should **not** be given peripherally

Central Access
-Epinephrine: 1 mg/mL

60 – minute mark

Subsequent Resuscitation
- Establish second PIV (or IO if PIV cannot be established) and consider central line.
- Administer 2nd and 3rd boluses* of 20 mL/kg isotonic saline or colloid up to and over 60 mL/kg until perfusion improves or unless rales or hepatomegaly develop
- Correct hypoglycemia† and/or hypocalcemia
- Consider treatment of anemia
- If on chronic steroids, give stress dose.
-Reassess need for additional fluid resuscitation

†Hypoglycemia Treatment
D10W 5 ml/kg/dose IV/IO
D25 2 ml/kg/dose IV/IO
D25 should be administered for children > 1 year old.

Clinical improvement

Yes →
- OFF algorithm
- Manage as appropriate to clinical findings
- Determine appropriate level of care‡

No →

Fluid Refractory Shock#
- Transfer to ICU‡
- Tailor vasopressor treatment based upon the patient's hemodynamic state. Epinephrine or norepinephrine can be started at the doses below.
  - Titrate epinephrine (dose range: EPINEPHrine 0.05 to 1 mcg/kg/min) via IV or central access.
  - Titrate central norepinephrine (dose range: 0.05 to 2 mcg/kg/min) via central access
- Obtain central access if it does not delay admission to the ICU. Initiate venous saturation and central venous pressure monitoring

Clinical improvement

Yes → OFF algorithm
Manage as appropriate to clinical findings

No

Catecholamine Resistant Shock
- Begin hydrocortisone if at risk for absolute adrenal insufficiency (Dosage: 2 mg/kg IV bolus). Obtain serum cortisol level prior to administration, if feasible.
-Consider ECMO if prior interventions are not effective

‡ICU Transfer Criteria
- Vital signs and/or neurological signs every hour or more frequent as ordered
- Intubation and/or acute ventilatory assistance
- Vasoactive drugs to maintain cardiovascular status
- Clinical concern for deterioration
- Arterial Cannulation

References

1. Biban, P., Gaffuri, M., Spaggiari, S., Zaglia, F., Serra, A., et al. (2012). Early recognition and management of septic shock in children. *Pediatric Reports, 4*, 48-51.
2. Melendez, E., & Bachur, R. (2006). Advances in the emergency management of pediatric sepsis. Current Opinion in Pediatrics, 18, 245-253.
3. Hartman, M., Linde-Zwirble, W., Angus, D., & Watson, R. S. (2013). Trends in the epidemiology of pediatric severe sepsis. *Pediatric Critical Care Medicine, 14*(7), 686-693.
4. Watson, R.S., Carcillo, J.A., Linde-Zwirble, W.T., Clermont, G., Lidicker, J. & Angus, D.C. (2003). The epidemiology of severe sepsis in children in the United States. *American Journal of Respiratory and Critical Care Medicine, 167*, 695-701.
5. Texas Children's Hospital EDW Qlikview. Retrieved June 26, 2014.
6. Gaines, N., Patel, B., Williams, E., & Cruz, A. (2012). Etiologies of septic shock in a pediatric emergency department population. *The Pediatric Infectious Disease Journal, 31*(11), 1203-1205.
7. American Heart Association & American Academy of Pediatrics. (2016). Pediatric Advanced Life Support: Provider Manual. Dallas, TX: American Heart Association.
8. Larsen, G.Y., Mecham, N. & Greenberg, R. (2011). An emergency department septic shock protocol and care guideline for children initiated at triage. *Pediatrics, 127*(6), e1585-e1592.
9. Kleinman, M.E., Chameides, L., Schexnayder, S.M. et al (2010). Part 14: Pediatric advanced life support: 2010 American heart association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation: Journal of the American Heart Association, 122,* S876-S908.
10. Brierley, J., Carcillo, J., Choong, K., Cornell, T., DeCaen, A., et al. (2009). Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. Critical Care Medicine, 37(2), 666-688.
11. Kissoon, N., Orr, R., & Carcillo, J. (2010). Updated American College of Critical Care Medicine- pediatric advanced life support guidelines for management of pediatric and neonatal septic shock. Pediatric Emergency Care, 26(11), 867-869.
12. Balamuth, F., Alpern, E., Grundmeier, R., Chilutti, M., Weiss, S. et al. (2015). Comparison of two sepsis recognition methods in a pediatric emergency department. *Academic Emergency Medicine, 22*, 1298-1306.
13. Fisher, J., Nelson, D., Beyersdorf, H., & Satkowiak, L. (2010). Clinical spectrum of shock in the pediatric emergency department. Pediatric Emergency Care, 26(9), 622-624.
14. Han, Y., Carcillo, J., Dragotto, M., Bills, D., Watson, R., et al. (2003). Early reversal of pediatric-neonatal septic shock by community physicians is associated with improved outcome. Pediatrics, 112(4), 793-799.
15. Scott, H., Donoghue, A., Gaieski, D., Marchese, R., & Mistry, R. (2014). Effectiveness of physical exam signs for early detection of critical illness in pediatric systemic inflammatory response syndrome. *Emergency Medicine*, 14, 1-6.
16. Cruz, A., Perry, A., Williams, E., Graf, J., Wuestner, E., et al. (2011). Implementation of goal-directed therapy for children with suspected sepsis in the emergency department. *Pediatrics, 127*(3), e758-e766.
17. Sebat, F., Johnson, D., Musthafa, A., Watnik, M., Moore, S., et al. (2005). A multidisciplinary community hospital program for early and rapid resuscitation of shock in nontrauma patients. *Chest, 127*(5), 1729-1743.
18. Shapiro, N., Howell, M., Talmor, D., Lahey, D., Ngo, L., et al. (2006). Implementation and outcomes of the multiple urgent sepsis therapies (MUST) protocol. *Critical Care Medicine, 34*(4), 1025-1032.
19. Akech, S., Ledermann, H., & Maitland, K. (2010). Choice of fluid for resuscitation in children with severe infection and shock: Systematic review. *British Medical Journal, 341:c4416*.
20. Bansal, M., Farrugia, A., Balboni, S., & Martin, G. (2013). Relative survival benefit and morbidity with fluids in severe sepsis – A network meta-analysis of alternative therapies. *Current Drug Safety, 8,* 236-245.
21. Carcillo, J., Kuch, B., Han, Y., Day, S., Greenwald, B. et al. (2009). Mortality and functional morbidity after use of PALS/APLS by community physicians. *Pediatrics, 124*(2), 500-508.
22. Chopra, A., Kumar, V., & Dutta, A. (2011). Hypertonic versus normal saline as initial fluid bolus in pediatric septic shock. *Indian Journal of Pediatrics, 78*(7), 833-837.
23. Delaney, A., Dan, A., McCaffrey, J., & Finfer, S. (2011). The role of albumin as a resuscitation fluid for patients with sepsis: A systematic review and meta-analysis. *Critical Care Medicine, 39*(2), 386-391.
24. Maitland, K., Kiguli, S., Opoka, R., Engoru, C., Olupot-Olupot, P., et al. (2011). Mortality after fluid bolus in African children with severe infection. *The New England Journal of Medicine, 364*(26), 2483-2495.
25. Oliveira, C., Nogueira de Sá, F., Oliveira, D., Gottschald, A., Moura, J., et al. (2008). Time- and fluid-sensitive resuscitation for hemodynamic support of children in septic shock. *Pediatric Emergency Care, 24*(12), 810-815.
26. Paul, R., Neuman, M., Monuteaux, M., & Melendez, E. (2012). Adherence to PALS sepsis guidelines and hospital length of stay. *Pediatrics, 130*(2), e273-e280.
27. Perel, P., Roberts, I., & Ker, K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database of Systematic Reviews 2013, Issue 2. Art. No: CD000567.
28. Santhanam, I., Sangareddi, S., Venkataraman, S., Kissoon, N., Thiruvengadamudayan, V. et al. A prospective randomized controlled study of two fluid regimens in the initial management of septic shock in the emergency department. Pediatric Emergency Care, 24(10), 647-655.
29. Stoner, M., Goodman, D., Cohen, D., Fernandez, S., & Hall, M. (2007). Rapid fluid resuscitation in pediatrics: Testing the American college of critical care medicine guideline. American College of Emergency Physicians, 50(5), 601-607.
30. De Backer, D., Aldecoa, C., Njimi, H., & Vincent, J. (2012). Dopamine versus norepinephrine in the treatment of septic shock: A meta-analysis. *Critical Care Medicine, 40*(3), 725-730.
31. Avni, T., Lador, A., Leibovici, L., Paul, M., & Grossman, A. (2015). Vasopressors for the treatment of septic shock: Systematic review and meta-analysis. Plos-One, 10(8), e)129305.
32. Gamper, G., Havel, C., Arrich, J., Losert, H., Pace, N., et al. Vasopressors for hypotensive shock. Cochrane Database of Systematic Reviews 2016, Issue 2. Art. No.: CD003709.
33. Lampin, M., Rousseaux, J., Botte, A., Cremer, R., & Leclerc, F. (2012). Noradrenaline use for septic shock in children: doses, routes of administration and complications. Acta Paediatrica, 101, e426-e430.
34. Oba, Y., & Lone, N. (2014). Mortality benefit of vasopressor and inotropic agents in septic shock: A bayesian network meta-analysis of randomized controlled trials. Journal of Critical Care, 29, 706-710.

35. Ramaswamy, K., Singhi, S., Jarashree, M., Bansal, A., & Nallasamy, K. (2016). Double-blind randomized clinical trial comparing dopamine and epinephrine in pediatric fluid-refractory hypotensive septic shock. Pediatric Critical Care Medicine
36. Ventura, A., Shieh, H., Bousso, A., Goes, P., Cassia, I., et al. (2015). Double-blind prospective randomized controlled trial of dopamine versus epinephrine as first-line vasoactive drugs in pediatric septic shock. Critical Care Medicine,
37. Zhou, F., Mao, Z., Zeng, X., Kang, H., Liu, H., et al. (2015). Vasopressors in septic shock: A systematic review and network meta-analysis. Therapeutics and Clinical Risk Management, 11, 1047-1059.
38. Perez, D., Jordan, I., Esteban, E., Garcia-Soler, P., Murga, V., et al. (2014). Prognostic factors in pediatric sepsis study, from the Spanish Society of Pediatric Intensive Care. The Pediatric Infectious Disease Journal, 33(2), 152-157.
39. Díaz-Martín, A., Martínez-González, M., Ferrer, R., Ortiz-Leyba, C., Piacentini, E., et al. (2012). Antibiotic prescription patterns in the empiric therapy of severe sepsis: Combination of antimicrobials with different mechanisms of action reduces mortality. *Critical Care, 16*:R223
40. Micek, S., Johnson, M., Reichley, R., & Kollef, M. (2012). An institutional perspective on the impact of recent antibiotic exposure on length of stay and hospital costs for patients with gram-negative sepsis. *BMC Infectious Diseases, 12*:56
41. Manji, A., Lehrnbecher, T., Dupuis, L., Beyene, J., & Sung, L. (2012). A systematic review and meta-analysis of anti-pseudomonal penicillins and carbapenems in pediatric febrile neutropenia. *Support Care Cancer, 20*, 2295-2304.
42. Manji, A., Lehrnbecher, T., Dupuis, L., Beyene, J., & Sung, L. (2012). A meta-analysis of antipseudomonal penicillins and cephalosporins in pediatric patients with fever and neutropenia. *The Pediatric Infectious Disease Journal, 31*(4), 353-359.
43. Sung, L., Manji, A., Beyene, J., Dupuis, L., Alexander, S., Phillips, R., et al. (2012). Fluoroquinolones in children with fever and neutropenia: A systematic review of prospective trials. *The Pediatric Infectious Disease Journal, 31*(5), 431-435.
44. Texas Children's Hospital Susceptibility Data. (2014). Antibiotic susceptibility in gram negative organisms for 53 individual patient isolates in the hematology/oncology population. Available from the TCH Pathology Database.
45. Annane, D., Bellissant, E., Bollaert, P., Briegel, J., Keh, D., et al. Corticosteroids for treating sepsis. Cochrane Database of Systematic Reviews 2015, Issue 12. Art. No.:CD002243.
46. Atkinson, S., Cvijanovich, N., Thomas, N., Allen, G., Anas, N., et al. (2014). Corticosteroids and pediatric septic shock outcomes: A risk stratified analysis. PLOS ONE, 9(11), 1-7.
47. Menon, K., McNally, D., Choong, K., & Sampson, M. (2013). A systematic review and meta-analysis on the effect of steroids in pediatric shock. Pediatric Critical Care Medicine, 14(5), 474-480.
48. Valoor, H., Singhi, S., & Jayashree, M. (2009). Low-dose hydrocortisone in pediatric septic shock: An exploratory study in a third world setting. Pediatric Critical Care Medicine, 10(1), 121-125.
49. Xu, S., Tang, Y., Song, H., Yang, S., Xu, W., et al. (2014). Corticosteroid administration is associated with improved outcome of patients presenting high inflammatory cytokine levels during septic shock. Pediatric Blood Cancer, 61, 2243-2248.
50. Karam, O., Tucci, M., Ducruet, T., Lacroix, J. et al. (2011). Red blood cell transfusion thresholds in pediatric patients with sepsis*. Pediatric Critical Care Medicine, 12(5), 512-518.
51. Angeletti, S., Spoto, S., Fogolari, M., Cortigiani, M., Fioravanti, M., et al. (2015). Diagnostic and prognostic role of procalcitonin (PCT) and MR-pro-Adrenomedullin (MR-proADM) in bacterial infections. APMIS, 123, 740-748.
52. Carrol, E., Newland, P., Thomson, A., & Hart, C. (2005). Prognostic value of procalcitonin in children with meningococcal sepsis. Critical Care Medicine, 33(1), 224-225.
53. Fioretto, J., Borin, F., Bonatto, R., Ricchetti, S., Kurokawa, C., et al. (2007). Procalcitonin in children with sepsis and septic shock. Jornal de Pediatria, 83(4), 323-328.
54. Fioretto, J., Martin, J., Kurokawa, C., Carpi, M., Bonatto, et al. (2010). Comparison between procalcitonin and C-reactive protein for early diagnosis of children with sepsis or septic shock. Inflammation Research, 59, 581-586.
55. Han, Y., Doughty, L., Kofos, D., Sasser, H., & Carcillo, J. (2003). Procalcitonin is persistently increased among children with poor outcome from bacterial sepsis. Pediatric Critical Care, 4(1), 21-25.
56. Hatherill, M., Tibby, S., Turner, C., Ratnavel, N., & Murdoch, I. (2000). Procalcitonin and cytokine levels: Relationship to organ failure and mortality in pediatric septic shock. Critical Care Medicine, 28(7), 2591-2594.
57. Jat, K., Jhamb, U., & Gupta, V. (2011). Serum lactate levels as the predictor of outcome in pediatric septic shock. Indian Journal of Critical Care Medicine, 15(2), 102-107.
58. Kim, Y., Ha, E., Jhang, W., & Park, S. (2013). Early blood lactate area as a prognostic marker in pediatric septic shock. Intensive Care Medicine. 39, 118-1823.
59. Rey, C., Los Arcos, M., Concha, A., Medina, A., Prieto, S., et al. (2007). Procalcitonin and C-reactive protein as markers of systemic inflammatory response syndrome severity in critically ill children. Intensive Care Medicine, 33, 477-484.
60. Sauer, M., Tiede, K., Fuchs, D., Gruhn, B., Berger, D., et al. (2003). Procalcitonin, C-reactive protein, and endotoxin after bone marrow transplantation: Identification of children at risk of morbidity and mortality from sepsis. Bone Marrow Transplantation, 31, 1137-1142.
61. Scott, H., Donoghue, A., Gaieski, D., Marchese, R., & Mistry, R. (2012). The utility of early lactate testing in undifferentiated pediatric systemic inflammatory response syndrome. *Academic Emergency Medicine, 19*, 1276-1280.
62. Van der Kaay, D., Kleijn, E., Rijke, Y., Hop, E., Groot, R., et al. (2002). Procalcitonin as a prognostic marker in meningococcal disease. Intensive Care Medicine, 28, 1606-1612.
63. Dursun, O., Hazar, V., Karasu, G., Uygun, V., Tosun, O., et al. (2009). Prognostic factors in pediatric cancer patients admitted to the pediatric intensive care unit. *Journal of Pediatric Hematology/Oncology, 31*, 481-484.
64. Leteurtre, S., Leclerc, F., Martinot, A., Cremer, R., Fourier, C., et al. (2001). Can generic scores (pediatric risk of mortality and pediatric index of mortality) replace specific scores in predicting the outcome of presumed meningococcal septic shock in children? *Critical Care Medicine, 29*(6), 1239-1246.
65. Rousseaux, J., Grandbastien, B., Dorkenoo, A., Lampin, M., Leteurtre, S., et al. (2013). Prognostic value of shock index in children with septic shock. *Pediatric Emergency Care, 29*, 1055-1059.
66. TCH Drug Information and Formulary, 12th Ed. http://www.crlonline.com/lco/action/home/switch

Clinical Standards Preparation

This clinical standard was prepared by the Evidence-Based Outcomes Center (EBOC) team in collaboration with content experts at Texas Children's Hospital. Development of this clinical standard supports the TCH Quality and Patient Safety Program initiative to promote clinical standards and outcomes that build a culture of quality and safety within the organization.

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Development Process

This clinical standard was developed using the process outlined in the EBOC Manual. The literature appraisal documents the following steps:

1. Review Preparation
   - PICO questions established
   - Evidence search confirmed with content experts

2. Review of Existing Internal and External Guidelines
   - Pediatric Basic and Advanced Life Support: 2010 - American Heart Association; Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock: 2007 Update from the American College of Critical Care Medicine; Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock 2012; Pediatric Basic Life Support and Pediatric Advanced Life Support: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations

3. Literature Review of Relevant Evidence
   - Searched: Medline, Cochrane, AHRQ, Cinahl, AAP, Google Scholar, American College of Critical Care Medicine, American Heart Association, Guideline Clearing House

4. Critically Analyze the Evidence
   - Three systematic reviews, eleven meta-analyses, six randomized controlled trials, thirty-six non-randomized studies, four professional organization guidelines

5. Summarize the Evidence
   - Materials used in the development of the guideline, evidence summary, and order sets are maintained in a Septic Shock evidence-based review manual within EBOC.

Evaluating the Quality of the Evidence

Published clinical guidelines were evaluated for this review using the **AGREE II** criteria. The summary of these guidelines are included in the literature appraisal. AGREE II criteria evaluate Guideline Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity and Presentation, Applicability, and Editorial Independence using a 4-point Likert scale. The higher the score, the more comprehensive the guideline.
This clinical standard specifically summarizes the evidence *in support of* or *against* specific interventions and identifies where evidence is *lacking/inconclusive*. The following categories describe how research findings provide support for treatment interventions.
"Evidence Supports" provides clear evidence that the benefits of the intervention exceed harm.
"Evidence Against" provides clear evidence that the intervention is likely to be ineffective or that it is harmful.
"Evidence Lacking/Inconclusive" indicates there is currently insufficient data or inadequate data to support or refute a specific intervention.
The **GRADE** criteria were utilized to evaluate the body of evidence used to make practice recommendations. The table below defines how the quality of the evidence is rated and how a strong versus weak recommendation is established. The literature appraisal reflects the critical points of evidence.

Recommendation	
STRONG	Desirable effects clearly outweigh undesirable effects or vice versa
WEAK	Desirable effects closely balanced with undesirable effects
Quality	**Type of Evidence**
High	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
Moderate	Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies
Low	Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence
Very Low	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

Recommendations

Practice recommendations were directed by the existing evidence and consensus amongst the content experts. Patient and family preferences were included when possible. The Content Expert Team and EBOC team remain aware of the controversies in the recognition and initial management in children. When evidence is lacking, options in care are provided in the clinical standard and the accompanying order sets (if applicable).

Approval Process

Clinical standards are reviewed and approved by hospital committees as deemed appropriate for its intended use. Clinical standards are reviewed as necessary within EBOC at Texas Children's Hospital. Content Expert Teams are involved with every review and update.

Disclaimer

Practice recommendations are based upon the evidence available at the time the guideline was developed. Clinical standards (guidelines, summaries, or pathways) do not set out the standard of care, and are not intended to be used to dictate a course of care. Each physician/practitioner must use his or her independent judgment in the management of any specific patient and is responsible, in consultation with the patient and/or the patient family, to make the ultimate judgment regarding care.

Version History

Date	Action	Comments
May 2015	First Iteration	
Jan 2017	Revision and Update	Vasopressor evidence update
Jan 2018	Revision	Change to antibiotic dosing
Jan 2019	Revision	Vital Signs Table Update
August 2021	Revision and Update	