Table 3: Evidence for Timely Fluid Bolus for Treatment of Children with Severe Sepsis or Septic Shock

Type of Evidence	Key Findings	Level of Evidence (USPSTF Ranking*)	Citations
Clinical guidelines	Pediatric considerations in severe sepsis: 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) transfusion is considered superior to crystalloid or albumin bolus. [p. 614]	III	Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013; 41(2): 580-637.

Type of Evidence	Key Findings	Level of Evidence (USPSTF Ranking*)	Citations
Clinical guidelines	ABCs for the first hour of resuscitation for pediatric septic shock: Goals include maintenance or restoration of circulation, defined as normal perfusion and blood pressure; maintenance or restoration of threshold heart rate. Fluid resuscitation should begin immediately unless hepatomegaly/rales are present. (Recall that rales may be heard in children with pneumonia as a cause of sepsis, so it does not always imply that the patient is fluid overloaded). If pneumonia is suspected or confirmed, fluid resuscitation should proceed with careful monitoring of the child's work of breathing and oxygen saturation. Rapid fluid boluses of 20 mL/kg (isotonic crystalloid or 5% albumin) can be administered by push or rapid infusion device (pressure bag) while observing for signs of fluid overload (i.e., the development of increased work of breathing, rales, gallop rhythm, or hepatomegaly). In the absence of these clinical findings, repeated fluid boluses can be administered to as much as 200 mL/kg in the first hour. Children commonly require 40 to 60 mL/kg in the first hour. Fluid can be pushed with the goal of attaining normal perfusion and blood pressure.	III	Brierley J, Carcillo JA, 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(2):666-688
Clinical guidelines	Rapid fluid boluses of 20 mL/kg (isotonic saline or colloid) should be administered by push while observing for the development of rales, gallop rhythm, hepatomegaly, and increased work of breathing. In the absence of these clinical findings, fluid can be administered to as much as 200 mL/kg in the first hour. Fluid should be pushed with the goal of attaining normal perfusion and blood pressure. [p. 1371]	III	Carcillo JA, Fields AI, et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock. *Crit Care Med* 2002; 30(6):1365-1378

Type of Evidence	Key Findings	Level of Evidence (USPSTF Ranking*)	Citations
Clinical guidelines	The choice of fluid is less important than the volume of fluid administered, as the latter sustains cardiac preload, increases stroke volume, and improves oxygen delivery. [p. 247] There is no clearly defined end point in fluid resuscitation in the absence of a measurement of central venous pressure (CVP) or signs of fluid overload. Administration of 20 mL/kg of isotonic saline/lactated Ringer's as an initial bolus is recommended. This may be repeated twice more (total 60 mL/kg) over 15-30 minutes as clinically indicated by the hemodynamic status. Fluid refractory shock is defined as the persistence of signs of shock after administration of sufficient fluids to have achieved a CVP of 8-12 mmHg and/or signs of fluid overload. If the patient still shows signs of shock, additional therapy such as vasopressors should be administered while diagnostic and therapeutic interventions are being performed.	III	Melendez E, Bachur R. Advances in the emergency management of pediatric sepsis. *Curr Opin Pediatr* 2006; 18:245-253.
Clinical protocol	Once severe sepsis or septic shock has been identified, the highest management priorities are establishing vascular access and initiating fluid resuscitation to improve tissue perfusion. Maintenance of tissue perfusion is critical, because global tissue hypoxia is a key step toward multiple organ failure [p.s18]	III	Rivers EP, Ahrens T. Improving outcomes for severe sepsis and septic shock: Tools for early identification of at-risk patients and treatment protocol implementation. *Crit Care Clin* 2008; S1-S47.

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Retrospective multicenter study	An analysis of mortality rates for children with severe sepsis and septic shock in relation to time-sensitive fluid resuscitation demonstrated the impact of early fluid resuscitation on shock reversal. Early volume replacement was associated with improved outcome. Greater amount of fluid received in the first hour was associated with decreased mortality, suggesting that restoration of adequate intravascular volume to improve tissue oxygen delivery can attenuate the inflammatory response and enhance outcomes. [p. 813]	III	Oliveira CF, Nogueira de Sá FR, Oliveira DSF, et al. Time- and fluid-sensitive resuscitation for hemodynamic support of children in septic shock: Barriers to the implementation of the American College of Critical Care Medicine/Pediatric Advanced Life Support Guidelines in a pediatric intensive care unit in a developing world. Pediatr Emerg Care 2008; 24(12):810-815

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Clinical protocol	Patients with sepsis and tissue hypoperfusion appear to benefit from a rapid bolus of intravenous crystalloid solution of at least 20 mL/kg. Further fluid resuscitation should be guided by the response to fluid loading. A positive response can be considered as one of the following: >10% increase of systolic/mean arterial blood pressure; >10% reduction of heart rate; and/or improvement of mental state, peripheral perfusion, and/or urine output. Fluid amounts as high as 110 mL/kg may be required in children with septic shock during early resuscitation. In children with profound anemia and severe sepsis, fluid boluses must be administered cautiously, and blood transfusions should be considered. Fluid resuscitation should be stopped or interrupted when no improvement of tissue perfusion occurs in response to volume loading. Development of crepitations (rales) or hepatomegaly in children indicates fluid overload or impaired cardiac function. Since aggressive fluid resuscitation can lead to respiratory impairment, additional fluid resuscitation following the initial fluid boluses should be performed carefully if no mechanical ventilator is available. [p. 559-560] Fluid administration in patients with sepsis should be accomplished via the intravenous or intra-osseous route.	III	Dünser MW, Festic E, Dondorp A, et al. Recommendations for sepsis management in resource-limited settings. *Intensive Care Med* 2012; 38:557-574.

Note: *USPSTF criteria for assessing evidence at the individual study level are as follows: I) Properly powered and conducted randomized controlled trial (RCT); well-conducted systematic review or meta-analysis of homogeneous RCTs. II) Well-designed cohort or case-control analytic study. III) Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees.*