Table 4: Evidence for Prompt Antimicrobial Therapy 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: Empiric antibiotics should be administered within 1 hour 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 of choice should be changed as endemic ecologies dictate (e.g., H1N1, penicillin- resistant pneumococci, recent stay in an intensive care unit [ICU]). Because establishing vascular access is difficult in newborns and children, antimicrobials can be given intramuscularly or orally (if tolerated) until intravenous (IV) line access is obtained. [p. 615]	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.
Clinical guidelines	Antibiotics should be started within the first hours of recognition of sepsis. In children, antibiotics should not be delayed to obtain a specific specimen; but, at minimum, a blood culture should be obtained prior to antibiotics. In general, children should receive a broad-spectrum β-lactam antibiotic as monotherapy, or a combination of antibiotics that provide empiric coverage for pathogens expected for age and that penetrate the presumed source of the infection. A third-generation cephalosporin will usually provide sufficient empiric coverage as first-line therapy. The choice of empirical antibiotic coverage therapy depends on several factors related to the patient's history, which may include previous pathogens isolated, known colonization with specific pathogens, presence of underlying disease or foreign body, and the susceptibility patterns of microorganisms of the hospital environment and the patient's community. Children who are at risk of neutropenia, are immunocompromised, or immunosuppressed may have microbes that require selection of additional antibiotics. [p. 251]	III	Melendez E, Bachur R. Advances in the emergency management of pediatric sepsis. *Curr Opin Pediatr* 2006; 18:245-253.
Clinical protocol	Given the importance of timely antimicrobial treatment, delaying treatment to await culture results has negative consequences. Clinicians should be aware that blood cultures will be negative in more than 50% of severe sepsis/septic shock. Furthermore, restricting use of antibiotics to limit development of resistance or reduce cost is not appropriate in this patient population. Broad-spectrum therapy is	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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Clinical protocol (continued)	warranted until information (causative agent, antibiotic susceptibilities) is available for therapeutic adjustment. Selection of an appropriate anti-microbial agent, often in the absence of microbiological confirmation, requires consideration of patient-related characteristics, such as drug intolerance, recently used antibiotics, previous infections, underlying disease, and clinical syndrome. Awareness of the prevalence of infections caused by specific organisms can provide clinicians with insight into appropriate empiric antimicrobial therapy. Pathogen resistance patterns in the hospital and community, along with hospital protocols to limit antibiotic resistance, also should be taken into account. Clinicians should consider the setting-specific prevalence of oxacillin (methicillin)-resistant *Staphylococcus aureus* (ORSA and MRSA) and the possibility of candidemia when selecting an initial antibiotic therapy. Clinicians should also be aware of general microbial trends. [p. S21]	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
Retrospective multicenter study	This study in adults examined the relationship between the delay in the initiation of effective antimicrobial therapy from onset of recurrent or persistent hypotension and survival in septic shock. The main outcome measure was survival to hospital discharge. Among the 2154 septic shock patients (78.9% total) who received effective antimicrobial therapy only after the onset of recurrent or persistent hypotension, a strong relationship between the delay in effective antimicrobial initiation and in-hospital mortality was noted (adjusted odds ratio 1.119 per hour delay). Administration of an antimicrobial effective for isolated or suspected pathogens within the first hour of documented hypotension was associated with a survival rate of 79.9%. Each hour of delay in antimicrobial administration over the ensuing 6 hours was associated with an average decrease in survival of 7.6%. By the second hour after onset of persistent/recurrent hypotension, the in-hospital mortality rate was significantly increased relative to receiving therapy within the first hour. [p. 1589-1590]	II	Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; 34(6):1589-1596

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	IV antimicrobial therapy is one of the key treatments in septic patients. If IV access cannot be promptly attained in children, first dosages may be administered intramuscularly or by the oral or rectal route. Since the causative pathogen cannot be identified immediately, antimicrobial therapy must be started empirically. To ensure the therapy is effective against the causative microorganisms, it is vital to account for the likely pathogen spectrum. Adequate dosing is another important aspect of antimicrobial therapy. Considering the high risk of death associated with sepsis, antimicrobial drugs need to be administered at maximum recommended dosages during the initial phase. [p. 565]		Dünser MW, Festic E, Dondorp A, et al. Recommendations for sepsis management in resource-limited settings. *Intensive Care Med* 2012; 38:557-574.
Retrospective analysis	This study, which used the Surviving Sepsis Campaign database, demonstrates that delay in antibiotic administration has a significant negative impact on survival across all areas in the hospital and across levels of illness severity (organ dysfunction). The most important finding is the survival benefit associated with prompt antibiotic administration in severe sepsis and septic shock. [pp.1753-1754]	II	Ferrer R, Martin-Loeches I, Phillips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock in the first hour: Results from a guideline-based performance improvement program. Crit Care Med 2014; 42(8):1749-1755
Descriptive study	Since the prompt institution of a therapy that is active against the causative pathogen is one of the most important predictors of outcome, clinicians must establish a system for rapid administration of a rationally chosen drug or combination of drugs when sepsis or septic shock is suspected. The expanding number of antibacterial, antifungal, and antiviral agents available provides opportunities for effective empiric and specific therapy. However, to minimize the promotion of antimicrobial resistance and cost and to maximize efficacy, detailed knowledge of the likely pathogens and the properties of the available drugs is necessary for the intensivist. [p. S495] Establishing vascular access and initiating aggressive fluid resuscitation is the first priority when managing patients with severe sepsis or septic shock. However, prompt infusion of antimicrobial agents is also a logical strategy and may require additional vascular access ports. Establishing a supply of pre-mixed antibiotics in	III	Bochud P-Y, Bonten M, Marchetti O, Calandra T. Antimicrobial therapy for patients with severe sepsis and septic shock: An evidence-based review. *Crit Care Med* 2004; 32(11):S495-S512

Type of Evidence	Key Findings	Level of Evidence	Citation
	the emergency department or critical care unit for such urgent situations is an appropriate strategy for enhancing the likelihood that antimicrobial agents will be infused promptly. Staff should be cognizant that some agents require lengthy infusion time, whereas others can be rapidly infused or even administered as a bolus [p. S497] Summary Recommendations [p. S507]: • Antibiotic therapy should be started within the first hour of recognition of severe sepsis, after appropriate cultures have been obtained. • Initial empirical anti-infective therapy should include one or more drugs that have activity against the likely pathogens (bacterial or fungal) and that penetrate into the presumed source of sepsis. The choice of drugs should be guided by the susceptibility patterns of microorganisms in the community and the hospital. • Monotherapy is as efficacious as combination therapy with a β-lactam and an aminoglycoside as empirical therapy of patients with severe sepsis or septic shock • Third and fourth generation cephalosporins, carbpenems, and extended -spectrum carboxypenicillins or ureidopenicillins combined with β-lactamase inhibitors are equally effective as empirical antibiotics therapy in patients with severe sepsis. • Empirical antifungal therapy should not be used on a routine basis in patients with severe sepsis or septic shock, but may be justified in selected subsets of septic patients at high risk for invasive candidiasis.		

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.*