3. Administer Broad Spectrum Antibiotics

Related Measures
Timing of Antibiotics

Background
Once severe sepsis is identified, antibiotics must be started rapidly to treat the underlying infection. Although early antibiotic administration seems to be an intuitive approach, administration of effective therapies is often delayed. Evidence supports that for patients with septic shock, the duration of hypotension prior the administration of antibiotics is a critical determinant in the survival of septic shock.[1]

The balance of evidence unwaveringly suggests that early administration of appropriate antibiotics reduces mortality in patients with Gram-positive and Gram-negative bacteremias. Some of the evidence supporting early administration is based on the assumption that patients who fail to receive appropriate antibiotics essentially represent a set of patients for whom delay has occurred in antibiotic delivery. Several studies have confirmed the mortality benefit associated with appropriate antimicrobials in patients with severe infections due to Gram-negative and Gram-positive bacteria.[2-4]

In addition, the major sources of infection in severe sepsis or shock are pneumonia and intra-abdominal infections [5,6] and other sources generally account for <5 percent of cases. The prevalence of pneumonia as a cause of sepsis lends support to the case for treating severe sepsis with early antibiotic administration. In a study of ventilator-acquired pneumonia, patients with significant organ dysfunction (required criteria for severe sepsis) who received antibiotics later had far greater ICU mortality: 37 percent vs. 7 percent (p=0.006); hospital mortality: 44 percent vs. 15 percent (p=0.01).[7]

Choice of Antibiotics
The choice of antibiotics should be guided by the susceptibility of likely pathogens in the community and the hospital, as well as any specific knowledge about the patient, including drug intolerance, underlying disease, the clinical syndrome. The regimen should cover all likely pathogens since there is little margin for error in critically ill patients. There is ample evidence that failure to initiate appropriate therapy promptly (i.e., therapy that is active against the causative pathogen) has adverse consequences on outcome.[2-4]

Although restricting the use of antibiotics, and particularly broad spectrum antibiotics, is important for limiting superinfection and for decreasing the development of antibiotic resistant pathogens, patients with severe sepsis or septic shock warrant broad spectrum therapy until the causative organism and its antibiotic susceptibilities are defined.
Availability
Establishing a supply of premixed antibiotics in an 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 more lengthy infusion time, whereas others can be rapidly infused or even administered as a bolus.

48- to 72-Hour Re-evaluation
Once the causative agent and antibiotic susceptibilities have been identified, restriction of the number of antibiotics and narrowing the spectrum of antimicrobial therapy is an important and responsible strategy for minimizing the development of resistant pathogens and for containing costs.

The antimicrobial regimen should always be reassessed after 48 to 72 hours on the basis of microbiological and clinical data, with the aim of using a narrow-spectrum antibiotic to prevent the development of resistance, to reduce toxicity, and to reduce costs. Empiric combination therapy should not be administered for more than 3 to 5 days.[12-16] Once a causative pathogen is identified, there is no evidence that combination therapy is more effective than monotherapy. The duration of therapy should typically be 7 to 10 days and guided by clinical response. Longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with S. aureus, some fungal and viral infections, or immunologic deficiencies, including neutropenia.[17]

Dosing
All patients should receive a full loading dose of each antimicrobial. However, patients with sepsis or septic shock often have abnormal renal or hepatic function and may have abnormal volumes of distribution due to aggressive fluid resuscitation. The ICU pharmacist should be consulted to ensure that serum concentrations are attained that maximize efficacy and minimize toxicity.[8-11]

Grading the Evidence
The Grade 1 recommendations below reflect strong evidence for care based on a number of qualitative considerations. The Grade 2 suggestions below are weaker recommendations for care based on a number of qualitative considerations. “B” level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies. “C” level evidence reflects well-done observational or cohort studies with controls. “D” level evidence generally reflects case series data or expert opinion. “UG” level evidence is ungraded.

- Administer effective intravenous antimicrobials within the first hour of recognition of septic shock (Grade 1B) and severe sepsis without septic shock (Grade 1C) as the goal of therapy.

- Initial empiric anti-infective therapy of one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis (Grade 1B) should be employed.

- Antimicrobial regimen should be reassessed daily for potential deescalation (Grade 1B).
Use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection (Grade 2C).

Combination empirical therapy for neutropenic patients with severe sepsis (Grade 2B) and for patients with difficult-to-treat, multidrug-resistant bacterial pathogens such as Acinetobacter and Pseudomonas spp. (Grade 2B). For patients with severe infections associated with respiratory failure and septic shock, combination therapy with an extended spectrum beta-lactam and either an aminoglycoside or a fluoroquinolone is for P. aeruginosa bacteremia (Grade 2B). A combination of beta-lactam and macrolide for patients with septic shock from bacteremic Streptococcus pneumoniae infections (Grade 2B).

Empiric combination therapy should not be administered for more than 3 to 5 days. De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known (Grade 2B).

Duration of therapy is typically 7 to 10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainerable foci of infection, bacteremia with S. aureus, some fungal and viral infections, or immunologic deficiencies, including neutropenia (Grade 2C).

Antiviral therapy initiated as early as possible in patients with severe sepsis or septic shock of viral origin (Grade 2C).

Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of noninfectious cause (UG).

References


Content adapted extensively from:

**TIPS**

1. Establish a standardized clinical protocol that includes the empiric administration of antibiotics in severe sepsis within 1 hour of presentation.
2. Establish a pre-mixed quantity of broad spectrum antibiotics available in the emergency department and ICU, in order to avoid delays involving pharmacy acquisition of the antibiotic.
3. Infuse antibiotics through multiple lines as available in order to speed delivery of agents.
4. Cover both Gram-positive and Gram-negative organisms.
5. Consider specific knowledge about the patient’s past organism burden, if available (including fungal infection); the setting from which the patient arrived in the emergency department (e.g., another institution that may harbor resistant organism); and community and hospital resistance patterns in making choices.