TABLE 325-3 INITIAL ANTIMICROBIAL THERAPY FOR SEVERE SEPSIS WITH NO OBVIOUS SOURCE IN ADULTS WITH NORMAL RENAL FUNCTION

Clinical Condition	Antimicrobial Regimens (Intravenous Therapy)
Immunocompetent adult	The many acceptable regimens include (1) piperacillin-tazobactam (3.375 g q4–6h); (2) imipenem-cilastatin (0.5 g q6h), ertapenem (1 g q24h), or meropenem (1 g q8h); or (3) cefepime (2 g q12h). If the patient is allergic to β-lactam agents, use ciprofloxacin (400 mg q12h) or levofloxacin (500–750 mg q12h) plus clindamycin (600 mg q8h). Vancomycin (15 mg/kg q12h) should be added to each of the above regimens.
Neutropenia (<500 neutrophils/μL)	Regimens include (1) imipenem-cilastatin (0.5 g q6h) or meropenem (1 g q8h) or cefepime (2 g q8h) or (2) piperacillin-tazobactam (3.375 g q4h) plus tobramycin (5–7 mg/kg q24h). Vancomycin (15 mg/kg q12h) should be added if the patient has an indwelling vascular catheter, has received quinolone prophylaxis, or has received intensive chemotherapy that produces mucosal damage; if staphylococci are suspected; if the institution has a high incidence of MRSA infections; or if there is a high prevalence of MRSA isolates in the community. Empirical antifungal therapy with an echinocandin (for caspofungin: a 70-mg loading dose, then 50 mg daily), voriconazole (6 mg/kg q12h for 2 doses, then 3 mg/kg q12h), or a lipid formulation of amphotericin B should be added if the patient is hypotensive, has been receiving broad-spectrum antibacterial drugs, or remains febrile 5 days after initiation of empirical antibacterial therapy.
Splenectomy	Cefotaxime (2 g q6–8h) or ceftriaxone (2 g q12h) should be used. If the local prevalence of cephalosporin-resistant pneumococci is high, add vancomycin. If the patient is allergic to β-lactam drugs, vancomycin (15 mg/kg q12h) plus either moxifloxacin (400 mg q24h) or levofloxacin (750 mg q24h) should be used.
IV drug user	Vancomycin (15 mg/kg q12h) is essential.
AIDS	Cefepime alone (2 g q8h) or piperacillin-tazobactam (3.375 g q4h) plus tobramycin (5–7 mg/kg q24h) should be used. If the patient is allergic to β-lactam drugs, ciprofloxacin (400 mg q12h) or levofloxacin (750 mg q12h) plus vancomycin (15 mg/kg q12h) plus tobramycin should be used.

Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

Source: Adapted in part from DN Gilbert et al: *The Sanford Guide to Antimicrobial Therapy*, 43rd ed, 2013.

evidence of cholecystitis, bile duct dilation, and pus collections in the liver, subphrenic space, or spleen.

HEMODYNAMIC, RESPIRATORY, AND METABOLIC SUPPORT

The primary goals are to restore adequate oxygen and substrate delivery to the tissues as quickly as possible and to improve tissue oxygen utilization and cellular metabolism. Adequate organ perfusion is thus essential. Circulatory adequacy is assessed by measurement of arterial blood pressure and monitoring of parameters such as mentation, urine output, and skin perfusion. Indirect indices of oxygen delivery and consumption, such as central venous oxygen saturation, may also be useful. Initial management of hypotension should include the administration of IV fluids, typically beginning with 1–2 L of normal saline over 1–2 h. To avoid pulmonary edema, the central venous pressure should be maintained at 8–12 cmH_2O. The urine output rate should be kept at >0.5 mL/kg per hour by continuing fluid administration; a diuretic such as furosemide may be used if needed. In about one-third of patients, hypotension and organ hypoperfusion respond to fluid resuscitation; a reasonable goal is to maintain a mean arterial blood pressure of >65 mmHg (systolic pressure >90 mmHg). If these guidelines cannot be met by volume infusion, vasopressor therapy is indicated **(Chap. 326)**. Titrated doses of norepinephrine should be administered through a central catheter. If myocardial dysfunction produces elevated cardiac filling pressures and low cardiac output, inotropic therapy with dobutamine is recommended. Dopamine is rarely used.

In patients with septic shock, plasma vasopressin levels increase transiently but then decrease dramatically. Early studies found that vasopressin infusion can reverse septic shock in some patients, reducing or eliminating the need for catecholamine pressors. Although vasopressin may benefit patients who require less norepinephrine, its role in the treatment of septic shock seems to be a minor one overall.

CIRCI (see "Adrenal Insufficiency," above) should be strongly considered in patients who develop hypotension that does not respond to fluid replacement therapy. Hydrocortisone (50 mg IV every 6 h) should be given; if clinical improvement occurs over 24–48 h, most experts would continue hydrocortisone therapy for 5–7 days before slowly tapering and discontinuing it. Meta-analyses of recent clinical trials have concluded that hydrocortisone therapy hastens recovery from sepsis-induced hypotension without increasing long-term survival.

Ventilator therapy is indicated for progressive hypoxemia, hypercapnia, neurologic deterioration, or respiratory muscle failure. Sustained tachypnea (respiratory rate, >30 breaths/min) is frequently a harbinger of impending respiratory collapse; mechanical ventilation is often initiated to ensure adequate oxygenation, to divert blood from the muscles of respiration, to prevent aspiration of oropharyngeal contents, and to reduce the cardiac afterload. The results of recent studies favor the use of low tidal volumes (6 mL/kg of ideal body weight, or as low as 4 mL/kg if the plateau pressure exceeds 30 cmH_2O). Patients undergoing mechanical ventilation require careful sedation, with daily interruptions; elevation of the head of the bed helps to prevent nosocomial pneumonia. Stress-ulcer prophylaxis with a histamine H_2-receptor antagonist may decrease the risk of gastrointestinal hemorrhage in ventilated patients.

Erythrocyte transfusion is generally recommended when the blood hemoglobin level decreases to ≤7 g/dL, with a target level of 9 g/dL in adults. Erythropoietin is not used to treat sepsis-related anemia. Bicarbonate is sometimes administered for severe metabolic acidosis (arterial pH <7.2), but there is little evidence that it improves either hemodynamics or the response to vasopressor hormones. DIC, if complicated by major bleeding, should be treated with transfusion of fresh-frozen plasma and platelets. Successful treatment of the underlying infection is essential to reverse both acidosis and DIC. Patients who are hypercatabolic and have acute renal failure may benefit greatly from intermittent hemodialysis or continuous veno-venous hemofiltration.

GENERAL SUPPORT

In patients with prolonged severe sepsis (i.e., that lasting more than 2 or 3 days), nutritional supplementation may reduce the impact of protein hypercatabolism; the available evidence favors the enteral delivery route. Prophylactic heparinization to prevent deep venous thrombosis is indicated for patients who do not have active bleeding or coagulopathy; when heparin is contraindicated, compression