TERMINOLOGY

CLINICAL CLARIFICATION

- Sepsis is a life-threatening syndrome of organ dysfunction caused by microbial infection in conjunction with a dysregulated host response [1]
- Characterized by a cascade of endothelial damage, vascular permeability, microvascular dysfunction, and coagulopathies, which can lead to multiorgan failure and death if not treated promptly and adequately or if not responsive to treatment [2]

CLASSIFICATION

- Sepsis [1]
  - Life-threatening organ dysfunction caused by dysregulated host response to infection
  - Organ dysfunction is defined by increase from baseline in SOFA score of 2 or more (Sequential Organ Failure Assessment; originally the Sepsis-Related Organ Failure Assessment) [3, 1]
- Septic shock [1]
  - Subset of sepsis with profound circulatory and cellular/metabolic dysfunction and with significantly greater mortality risk
  - Defined as need for administration of vasopressor medication to maintain mean arterial pressure of at least 65 mm Hg and serum lactate level more than 2 mmol/L in the absence of hypovolemia [3, 1]

DIAGNOSIS

CLINICAL PRESENTATION

- History
  - Presentation is variable, depending on causative agent and portal of entry [4]
  - Low threshold of suspicion and early recognition of sepsis are essential for successful outcomes [4]
  - Thorough and timely history focuses on symptoms, comorbidities, recent surgery, recent antibiotic use, presence of medical devices, and travel [4]
  - Common generalized symptoms of sepsis include: [4]
    - Fever, chills; rigors may be reported
    - Confusion, anxiety
    - Fatigue, malaise
    - Myalgia
    - Dyspnea
    - Nausea and vomiting
    - Decreased urination
  - Localizing symptoms may include: [4]
    - Headache and stiff neck when meningitis is the cause of sepsis
    - Cough and pleuritic chest pain with pneumonia
    - Abdominal pain with gastrointestinal or genitourinary source
    - Diarrhea in gastrointestinal luminal infections, such as ***Clostridium difficile*** or toxigenic ***Escherichia coli*** infection
    - Flank pain and dysuria with kidney infection
    - Bone or joint pain with osteomyelitis or septic arthritis
    - Skin or soft tissue pain with abscesses, wounds, or other soft tissue infections
  - Elderly persons may have limited or nonspecific symptoms (eg, poor oral intake, inanition) [4]
- Physical examination
  - Physical examination focuses on detecting generalized signs of sepsis and on determining the source; a careful and thorough examination may uncover an unexpected site
  - Generalized evidence of sepsis is highly variable but commonly includes:
    - Fever (more than 38.5°C) or hypothermia (less than 36°C)
      - Fever is the most common sign of sepsis
    - Hypotension (systolic blood pressure lower than 90 mm Hg and/or mean arterial pressure lower than 70 mm Hg)
      - Presenting sign in 40% of patients with sepsis [4]
    - Tachycardia (heart rate more than 90 beats per minute)
    - Tachypnea (respiratory rate more than 20 breaths per minute)
    - Rigors may be observed
    - Altered mental status; older patients may present with irritability or agitation
    - Increased capillary refill time (more than 3 seconds)
    - Mottled skin on inspection; petechiae may be seen with severe thrombocytopenia or meningococcemia
    - Diaphoresis; clammy skin

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- Respiratory, gastrointestinal, and genitourinary systems and skin and soft tissue are the most common sites of infection leading to sepsis; signs specific to affected system include:
  - Respiratory
    - Cough; production of purulent or foul-smelling sputum may be observed by clinician or reported by patient
    - Hemoptysis may be observed by clinician or reported by patient with severe pneumonia, including tuberculosis
    - Dullness to percussion may indicate pleural effusion (parapneumonic effusion or empyema) or consolidation
    - Rhonchi and/or rales on auscultation
    - Egophony on auscultation indicates consolidation
  - Gastrointestinal
    - Abdominal distention on inspection
    - Decreased bowel sounds on auscultation owing to ileus
    - Abdominal pain with guarding on palpation; rigidity and rebound indicate peritonitis
      - Localization of tenderness may indicate source (eg, right upper quadrant for liver or gallbladder infection)
  - Genitourinary
    - Costovertebral tenderness and suprapubic pain on palpation
    - Vaginal discharge or bleeding
  - Skin and soft tissue
    - Wounds, ulcerations, furuncles, or carbuncles on inspection
      - In currently or recently hospitalized patients, surgical incisions and IV sites
    - There may be erythema and/or edema on inspection
    - Drainage may be evident, either spontaneous or expressed
    - Crepitus or fluctuancy may be palpable; an indurated tender phlebitic cord may be noted at site of infected peripheral IV line
    - Lymphadenopathy may be detected proximal to infection
  - Other less common findings may include:
    - Meningismus, Kernig sign, or Brudzinski sign in meningitis
    - Point tenderness over a vertebral body may indicate spinal osteomyelitis and/or epidural abscess
    - Warm, swollen joint may be a site of septic arthritis
    - New heart murmur or change in character of a murmur suggesting endocarditis

CAUSES AND RISK FACTORS

- Causes
  - Microbial pathogens breach skin and/or mucosal barriers to cause systemic infection
    - Wide range of microbial pathogens may be implicated, depending on site of primary infection, community patterns, and host characteristics
      - Most sepsis cases are caused by bacteria; fungi and viruses are less common causes but are significant causes of sepsis in immunocompromised patients
        - Gram-positive bacteria are responsible for most cases of septic shock in the acute care setting, followed by gram-negative and mixed bacterial infections
      - Candidal species are commonly implicated in neutropenic patients and in infections associated with indwelling catheters (eg, bloodstream, urinary) and other devices
      - Influenza virus may cause sepsis directly or may predispose to secondary bacterial infection and sepsis
    - Respiratory, gastrointestinal, and genitourinary systems and skin and soft tissue are the primary sites in most infections leading to sepsis (about 80%)[4]
      - Common source infections leading to sepsis include:
        - Respiratory tract infections (account for 35% of sepsis cases)[5]
          - Community-acquired pneumonia
            - ***Streptococcus pneumoniae*** and ***Staphylococcus aureus*** are commonly implicated in sepsis caused by pneumonia
            - Either may occur de novo or after influenza
          - Hospital-acquired and ventilator-associated pneumonias
            - Commonly associated with antibiotic-resistant pathogens
        - Genitourinary tract infections (account for 25% of sepsis cases)[5]
          - Usually gram-negative or enterococcal
            - Pyelonephritis
            - Cystitis
          - Infections related to indwelling urinary catheters
            - Antibiotic-resistant organisms are often implicated in hospital and long-term care settings

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        - Candidal species are common causes in patients with diabetes and in patients who have received broad-spectrum antibiotics
      - Obstruction of infected urine owing to impacted kidney stones or prostatic hypertrophy increases the risk of severe infection
    - Gastrointestinal tract infections (account for 11% of sepsis cases): often polymicrobial, involving enteric gram-negative bacilli, streptococcal species, and anaerobes[5]
      - Appendicitis, with or without perforation and abscess
      - Cholecystitis, cholangitis; biliary obstruction caused by gallstone impaction increases the risk of severe infection
      - Bowel infarction or perforation with peritonitis
      - Diverticulitis, with or without diverticular abscess
      - Pancreatitis may cause sepsis due to infection or may cause an inflammatory response that mimics sepsis
    - Skin and soft tissue infections (account for 11%[5] of sepsis cases)
      - Cellulitis
        - Usually caused by ***Staphylococcus aureus*** or streptococci
          - Community-acquired MRSA infection is prevalent in many areas
          - Presentation of MRSA is often characterized by deep red or violaceous erythema surrounding a necrotic center, resembling a spider bite
      - Carbuncles
        - Usually ***Staphylococcus aureus***
      - Wounds (traumatic or surgical)
        - Traumatic wounds can be infected with a variety of organisms, depending on the circumstances
          - Highly resistant ***Acinetobacter baumannii*** infections have been associated with combat wounds
        - Surgical wound infections may reflect nature of surgery (eg, colon surgery may be complicated by infection caused by enteric pathogens) or may be caused by common skin organisms
          - Antibiotic resistance is common
      - Infections related to intravascular access devices
        - May be isolated to insertion site, but secondary bacteremia is common in sepsis
        - Usually gram-positive organisms (***Staphylococcus aureus***, coagulase-negative staphylococci), but gram-negative bacilli or yeast are also common pathogens
      - Necrotizing fasciitis
        - Group A ***Streptococcus*** or synergistic polymicrobial infections are the most common causes of this unusual life-threatening condition
    - Less common but important sources of sepsis include:
      - Bone and joint infections
        - Osteomyelitis
          - Wide variety of pathogens, depending on cause (hematogenous versus contiguous focus)
        - Septic arthritis
          - Common causes vary with age; overall, ***Staphylococcus aureus*** and streptococci are the most common causes
      - Central nervous system infections
        - Meningitis
          - Typical pathogens vary by age range; ***Streptococcus pneumoniae*** and ***Neisseria meningitidis*** are the most common
        - Encephalitis
          - Usually viral; HSV and West Nile virus have been associated with sepsis
        - Epidural abscess
          - Uncommon; spinal epidural abscesses are usually secondary to bacteremia, with ***Staphylococcus aureus*** as the most frequent pathogen[6]

- Risk factors and/or associations
  - Age
    - Elderly people are at increased risk for sepsis and sepsis-associated hospitalizations, owing to comorbidities, medical interventions, institutionalization, immunosenescence, functional disability, and malnutrition[7]
      - About half of patients with sepsis are aged 65 years or older[8]
      - Sepsis hospitalization rate increases with age[9]
        - For those younger than 65 years: about 10 per 10,000 population[9]
        - For those aged 65 years or older: about 120 per 10,000 population[9]
        - For the oldest elderly (aged 85 years or older): about 270 per 10,000 population[9]

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- Infants are at increased risk for sepsis [10]
  - Incidence of sepsis in infants is higher than in overall population and pediatric population (about 50 per 10,000 population) [11]
  - Associated with prematurity, low birth weight, and maternal group B streptococcal infection [10]
- Sex
  - Males are 25% to 30% more likely to develop sepsis than females [12]
  - Males are more likely to develop sepsis due to respiratory tract infection than females; females are more likely to develop sepsis due to genitourinary tract infection [12]
- Genetics
  - Interleukin 1β-511 homozygosity is associated with increased risk of mortality from sepsis [13]
  - Genetic mutations leading to deficiency of mannose-binding lectin are associated with increased risk of sepsis, particularly pneumococcal sepsis [13]
  - Other hypotheses related to genetic predisposition to sepsis have been considered but are as yet unproven [13]
- Ethnicity/race
  - African Americans are twice as likely to develop sepsis compared with white Americans; African Americans have a higher case fatality rate than white Americans [12, 14]
    - Likely caused by interaction between differences in incidence of chronic comorbidities, socioeconomic factors, and genetics [14, 12]
  - Hispanic ethnicity is associated with a lower incidence of sepsis and a lower case fatality rate compared with African Americans; rates among Hispanic Americans are similar to those of white Americans [14]
- Other risk factors/associations
  - Factors that breach natural barriers to pathogen invasion or compromise immune function increase the risk of sepsis [4, 13, 15, 12]
    - Recent surgery or hospitalization
    - Indwelling urinary catheters
    - Intravascular access devices
    - Endotracheal tubes
    - Malnutrition
    - Burns and/or trauma
    - Chronic illness (eg, cancer, diabetes)
    - Immunosuppression (eg, immunosuppressive medical therapy, HIV infection)
    - IV drug use [15]
    - Pregnancy or recent childbirth, miscarriage, or termination of pregnancy—particularly if the following are present: [15]
      - Immunodeficiency
      - Diabetes or gestational diabetes
      - Invasive procedures such as cesarean or forceps delivery
      - Prolonged rupture of membranes
      - Close contact with people with group A streptococcal infection
      - Continued vaginal bleeding or offensive discharge

DIAGNOSTIC PROCEDURES

- Primary diagnostic tools
  - Diagnosis is based primarily on history and physical examination, coupled with laboratory results providing evidence for an inflammatory process and a microbial infection
  - Presence of organ dysfunction, integral to the diagnosis of sepsis, can be identified as an increase from baseline of 2 points or more in SOFA score (Sequential Organ Failure Assessment; originally the Sepsis-Related Organ Failure Assessment) [1]
    - qSOFA score (Quick Sequential Organ Failure Assessment or Quick Sepsis-Related Organ Failure Assessment) does not require laboratory testing and is as accurate as the full tool in non-ICU patients
    - Score is more specific than sensitive: a negative test result does not rule out sepsis and should not be considered a barrier to further testing and monitoring when diagnosis is suspected [16]
  - Initial laboratory tests in all patients include a CBC with differential; a metabolic panel; creatinine, bilirubin, and lactate levels; coagulation tests; blood gas levels; and urinalysis [4, 1]
    - Elements of SOFA score include platelet count, bilirubin level, creatinine level, and PaO_2 [1]
    - Results should be obtained promptly; in particular, lactate level should be measured within 1 hour of presentation with possible sepsis [17]
  - In all patients, obtain blood cultures and cultures from any suspected source of infection; do this before the first dose of antimicrobial therapy if that can be done without significant delay (less than 45 minutes) [18]

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- Additional laboratory tests may provide etiologic information (eg, rapid influenza antigen testing; 1,3-β-D-glucan assay; legionella and pneumococcal antigens)[4, 18]
- Perform imaging (eg, radiography, ultrasonography, CT, MRI) to confirm suspected anatomic site of infection; specific imaging mode to select depends on suspected site[19]
- Measurement of mean arterial pressure is indicated in patients with persistent hypoperfusion after fluid challenge[18]
  - May provide support for the diagnosis of sepsis, and forms a baseline to guide fluid and vasopressor treatment
- Several serum markers have been suggested as indicators of sepsis (eg, procalcitonin, C-reactive protein), but their role remains unclear in both diagnosis and management[20, 21]

- Laboratory
  - CBC[19]
    - Infection is suggested by a WBC count higher than 12,000 cells/mm³ or lower than 4000 cells/mm³, or by immature WBCs constituting more than 10% of the total
    - Platelet count lower than 100,000 cells/mm³ suggests hypoperfusion and organ dysfunction; may precede disseminated intravascular coagulation
  - Metabolic and chemistry panels[19]
    - Blood glucose level higher than 140 mg/dL in a patient without diabetes suggests injury or illness (including sepsis)
    - Creatinine level increase of 0.5 mg/dL or more suggests renal impairment and hypoperfusion; level greater than 2 mg/dL suggests sepsis
    - Elevated liver enzyme levels and/or bilirubin level greater than 2 mg/dL suggest hepatic impairment and hypoperfusion
  - Lactate level
    - Elevated serum lactate level is both diagnostic and prognostic for sepsis, as it suggests end-organ dysfunction
      - Obtain within 1 hour of clinical suspicion of sepsis; longer intervals are associated with delays in administration of fluids and antibiotics, and with higher mortality rates[17]
      - Followed serially in protocols for goal-directed therapy for sepsis
    - Low lactate level (0-2.5 mmol/L) is associated with a mortality rate of 4.9%[2]
    - Intermediate lactate level (2.5-3.9 mmol/L) is associated with a mortality rate of 9%[2]
    - High lactate level (greater than 4 mmol/L) is associated with a mortality rate of 28.4%[2]
  - Coagulation tests[19]
    - INR greater than 1.5 suggests coagulopathy associated with organ dysfunction
    - Activated partial thromboplastin time greater than 60 seconds suggests coagulopathy associated with organ dysfunction
  - Urinalysis and urine output
    - Provides assessment of renal function and fluid balance
    - Pyuria suggests urinary tract infection as the source of sepsis
    - Urine output less than 0.5 mL/kg/hour for more than 2 hours despite fluid resuscitation suggests hypoperfusion and/or renal dysfunction[19]
  - Cultures to determine pathogen and susceptibility to antibiotics
    - Blood cultures
      - Obtain specimens before starting broad-spectrum antimicrobial therapy provided that obtaining them does not cause a significant delay in administration of antimicrobials (ie, 45 minutes)[18]
      - Draw 2 sets of blood culture specimens, each for both aerobic and anaerobic incubation, from separate sites[18]
      - If vascular access devices are present and have been in place for 48 hours or more, draw culture specimens from each device if possible, as well as at least 1 peripheral set[18]
        - If the peripherally drawn specimen and the vascular access device–drawn specimen develop the same pathogen on culturing, the vascular access device is likely the source of sepsis
          - Culture positivity more than 2 hours earlier in the blood drawn from the device compared with the blood drawn simultaneously from another site has been suggested as evidence of device infection, but data are not conclusive
        - If the vascular access device was placed within 48 hours, culture from that site is not necessary
      - Blood culture results may be negative in 50% to 65% of patients with sepsis[4]
    - Urine cultures
      - Performed in conjunction with urinalysis in patients with suspected sepsis if urine is a possible source[19]
    - Stool culture
      - May be performed in patients with diarrhea who have been in the hospital for less than 72 hours; patients who have been in the hospital for more than 72 hours are not likely to have diarrhea caused by enteric pathogens
      - Additionally, consider tests for ***Clostridium difficile*** toxin in patients with diarrhea and recent antibiotic use

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  - Sputum culture
    - Performed in conjunction with Gram stain for suspected respiratory source of sepsis [19]
    - Mechanical ventilator use is associated with pneumonia and may be the source of sepsis
      - Quantitative cultures may help to discriminate between infection and colonization
  - Skin and soft tissue culture
    - Performed in conjunction with Gram stain on drainage from abscesses or surgical sites [19]
    - Culture of intact skin (eg, in cellulitis) is of little value and should not be done
  - Cerebrospinal fluid cultures
    - Done in conjunction with cell count and differential, chemistry, Gram stain, and other special tests as indicated
- Rapid influenza molecular testing on nasopharyngeal secretions is recommended for suspected influenza during periods of high influenza activity [22]
- Urine testing for legionella and pneumococcal antigens is advisable for patients with severe community-acquired pneumonia [22]
- Serum 1,3-β-D-glucan assay and mannan and antimannan antibody assays are recommended for suspected fungal sepsis [18]

- Imaging
  - Radiography
    - Chest radiography is used to confirm the presence of pneumonia
    - Abdominal radiography identifies bowel perforation by the presence of free air; it may also provide preliminary imaging clues for other causes of sepsis by demonstrating the presence of gallstones, kidney stones, or other abnormalities that can be further explored with other tests
    - Plain radiographs may also be of value in demonstrating the presence of air in soft tissues (eg, necrotizing infections) or osteomyelitis
  - Ultrasonography
    - Abdominal ultrasonography is used to identify abdominal infections (eg, appendicitis, cholecystitis, pancreatitis) [23]
    - Renal ultrasonography is used to identify renal obstruction or pyelonephritis
    - Echocardiography is used to identify endocarditis in patients with a cardiac murmur or suspected IV drug use
  - CT
    - CT of chest to confirm pneumonia as the source infection if chest radiography is not diagnostic
    - CT of abdomen and pelvis to identify abdominal or pelvic abscesses (eg, pancreatic abscess, renal abscess) or ischemic bowel
    - CT may also be used to determine depth and extent of some serious soft tissue infections (eg, necrotizing fasciitis)
  - MRI
    - MRI of brain and/or spine is used in evaluation of meningitis, encephalitis, and epidural abscess
- Functional testing
  - SOFA score (Sequential Organ Failure Assessment; originally the Sepsis-Related Organ Failure Assessment) [1]
    - Either the standard score or the quick version (qSOFA) is recommended for all patients to identify organ dysfunction, a defining feature of sepsis
    - In the standard version, assign points (0-4) for each of the following parameters:
      - PaO_2/FiO_2 ratio
        - 0 points: 400 or higher
        - 1 point: less than 400
        - 2 points: less than 300
        - 3 points: less than 200 with respiratory support
        - 4 points: less than 100 with respiratory support
      - Platelet count ($\times 10^3$ cells/mm^3)
        - 0 points: 150 or higher
        - 1 point: less than 150
        - 2 points: less than 100
        - 3 points: less than 50
        - 4 points: less than 20
      - Bilirubin level (mg/dL)
        - 0 points: less than 1.2
        - 1 point: 1.2 to 1.9
        - 2 points: 2 to 5.9
        - 3 points: 6 to 11.9
        - 4 points: 12 or higher

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- Mean arterial pressure/vasopressor requirement (given over at least 1 hour)
  - 0 points: 70 mm Hg or higher
  - 1 point: lower than 70 mm Hg
  - 2 points: dopamine dosage less than 5 mcg/kg/minute or any dose of dobutamine
  - 3 points: dopamine dosage 5.1 to 15 mcg/kg/minute or any dose of epinephrine
  - 4 points: dopamine dosage higher than 15 mcg/kg/minute ***or*** epinephrine dosage higher than 0.1 mcg/kg/minute ***or*** norepinephrine dosage higher than 0.1 mcg/kg/minute
- Glasgow Coma Scale score
  - 0 points: 15
  - 1 point: 13 to 14
  - 2 points: 10 to 12
  - 3 points: 6 to 9
  - 4 points: less than 6
- Creatinine level (mg/dL)
  - 0 points: lower than 1.2
  - 1 point: 1.2 to 1.9
  - 2 points: 2 to 3.4
  - 3 points: 3.5 to 4.9
  - 4 points: 5 or higher
- Urine output (mL/day)
  - 3 points: less than 500
  - 4 points: less than 200

– An increase from baseline of 2 points or more indicates presence of organ failure; if baseline is unknown, assume it to be 0

- qSOFA score (Quick Sequential Organ Failure Assessment or Quick Sepsis-Related Organ Failure Assessment)
  - Consists of 3 parameters. Presence of any 2 is indicative of organ dysfunction and possible sepsis:
    - Respiratory rate of 22 breaths per minute or faster
    - Altered mentation
    - Systolic blood pressure of 100 mm Hg or lower
- Measurement and monitoring central vein hemodynamic parameters is appropriate for patients with evidence of hypoperfusion (eg, hypotension that persists after fluid challenge)[18]
  - Mean arterial pressure
    - Calculation of average pressure in 1 cardiac cycle, and a measure of organ perfusion
    - Mean arterial pressure of less than 60 mm Hg suggests that tissue oxygen and nutrient needs are not being met

DIFFERENTIAL DIAGNOSIS

- Most common[4]
  - Hypovolemic or hemorrhagic shock
    - Rapid fluid loss resulting in inadequate circulating volume and hypoperfusion; most often caused by burns, trauma, gastrointestinal bleeding, and ruptured abdominal aortic aneurysm
    - Similar features: tachypnea, tachycardia, malaise, hypotension, hypoxia, decreased capillary refill, mottled skin, oliguria, pallor, and altered mental status
    - Differentiating features: absence of fever; abnormalities in WBC count are usually absent or minimal
    - Diagnosed by: history, physical examination, and imaging indicate source of hemorrhage or other volume loss
  - Pulmonary embolism[24]
    - Sudden occlusion of a pulmonary artery, most often caused by a dislodged thrombus
    - Similar features: dyspnea, tachypnea, hypoxia
    - Differentiating features: onset of symptoms is abrupt; pleuritic chest pain is common
    - Diagnosed by: multidetector-row CT angiography or CT pulmonary angiography detects pulmonary emboli; D-dimer levels are usually elevated
  - Myocardial infarction
    - Myocardial necrosis resulting from occlusion of a coronary artery
    - Similar features: dyspnea, fatigue
    - Differentiating features: retrosternal chest pain and/or pressure radiating to neck, jaw, shoulder, and/or arm
    - Diagnosed by: ECG shows ST elevation, ST depression, or T-wave inversion; cardiac troponin level is elevated
  - Acute pancreatitis[25]
    - Sudden onset of parenchymal and pancreatic fat necrosis with inflammation of pancreas
    - Similar features: fever, diaphoresis, nausea, vomiting

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  - Differentiating features: sudden onset of constant epigastric or left upper quadrant pain that may radiate to the back, chest, or flanks
  - Diagnosed by: serum amylase and lipase levels more than 3 times the upper reference limit, with confirmatory findings from abdominal imaging
- Diabetic ketoacidosis[26]
  - Decompensated state of diabetes that presents with the biochemical triad of hyperglycemia, ketonemia, and metabolic acidosis
  - Similar features: tachycardia, hypotension, weakness, nausea, vomiting
  - Differentiating features: polyuria, polydipsia, polyphagia, absence of fever, Kussmaul respirations, acetone breath
  - Diagnosed by: hyperglycemia, positive urine and serum ketones, decreased arterial pH, elevated anion gap, decreased serum bicarbonate level
- Adrenal insufficiency[27]
  - Cortisol and mineralocorticoid deficiency in primary adrenal insufficiency, or suppression of hypothalamic-pituitary axis in secondary adrenal insufficiency
  - Similar features: tachycardia, weakness, vomiting, hypotension, altered mental status
  - Differentiating features: increased skin pigmentation, salt craving, weight loss, more gradual progression of symptoms
  - Diagnosed by: decreased serum cortisol level, elevated adrenocorticotropic hormone level
- Transfusion reaction[28]
  - Adverse reaction to blood or blood product transfusion
  - Similar features: fever, rigors, dyspnea
  - Differentiating features: pruritus, urticaria, angioedema, evidence of hemolysis
  - Diagnosed by: history of blood transfusion and analysis of pretransfusion and posttransfusion blood samples

TREATMENT

GOALS

- Initial respiratory and hemodynamic stabilization to promote perfusion and maintain vital organ function
  - Within the first hour diagnosis is suspected:[17]
    - Begin fluid resuscitation for patients who are hypotensive or who have serum lactate levels of 4 mmol/L or higher
    - If hypotension persists during or after fluid resuscitation, start vasopressors immediately
- Initial antimicrobial treatment with broad-spectrum agents until the underlying infection is identified; tailored antimicrobial treatment once causative pathogen is identified
  - Within the first hour diagnosis is suspected, begin empiric therapy[17]
- Source control within the first 12 hours if possible
- Prevention of complications and sequelae

DISPOSITION

- Admission criteria
  - Sepsis requires inpatient acute care for monitoring, IV antimicrobial therapy, and supportive care
  - Criteria for ICU admission
    - Septic shock with hemodynamic instability requires ICU admission for hemodynamic monitoring and treatment[29]
- Recommendations for specialist referral
  - Refer to infectious disease specialist to identify cause and direct appropriate antimicrobial therapy
  - Consult clinical pharmacologist to optimize dosing regimen
  - Refer to critical care specialists to guide resuscitative efforts in septic shock
  - Additional specialist referral depends on cause of sepsis and/or organ dysfunction resulting from sepsis; may include cardiologist, pulmonologist, nephrologist, or gastroenterologist
  - Surgical referral may be required for source control of abdominal or necrotizing infections

TREATMENT OPTIONS

- Initial treatment often occurs in the emergency department and is continued in the inpatient setting; treatment should proceed rapidly (within 1 hour[17]), regardless of setting[18]
  - Implementation of multidisciplinary sepsis bundles that promote early identification and provide management protocols may result in improved outcomes[30, 17]
- Treatment includes immediate stabilization, fluid resuscitation, initiation of antimicrobials, hemodynamic support, and source control[18]
  - Ensure patency of airway and provide supplemental oxygen; support ventilation mechanically if necessary to improve oxygenation, protect airway, or prevent imminent respiratory failure[4]

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- Invasive monitoring of hemodynamic parameters is recommended for patients with septic shock, and it can be used in patients without shock to monitor response to fluids
  - Arterial catheter is recommended whenever possible in patients who are receiving vasopressors
- Establish adequate IV access (2 large-gauge IV devices, preferably 18-gauge or larger) and begin infusing crystalloid solution immediately upon suspicion of sepsis and either hypotension or a lactate level of 4 mmol/L or higher; the recommended goal is 30 mL/kg within 3 hours [18, 17]
  - Early goal-directed therapy, a core component of previous sepsis guidelines, has not been shown to improve mortality in more recent studies [31, 32, 33, 18]
  - Nevertheless, adequate fluid resuscitation is essential, and many patients require large volumes, depending on hemodynamic response
    - Normalization of lactate levels also may be used as a guide to adequate fluid resuscitation [34, 35]
    - Bedside cardiac ultrasonography and other techniques may be used to assess initial fluid responsiveness; serial follow-up studies may help to determine fluid repletion and indication for inotropic therapy [36]
  - Evidence and guidelines suggest that crystalloids should be used as first line fluid therapy; albumin may be needed for patients requiring large volumes of crystalloids [37, 38, 18]
  - Normal saline has typically been the primary IV fluid given; however, balanced crystalloid solutions, such as lactated Ringer solution, may have fewer adverse metabolic effects and a lower rate of complications [39]
- After collecting blood and other specimens for culture, but within the first hour [17] of recognizing sepsis or septic shock, begin antimicrobial therapy [18]
  - Immediate (within 1 hour) administration of antibiotics may reduce mortality by as much as 33% compared with later administration [40, 41]
  - Initial antimicrobial therapy is empiric
    - Begin with IV antiinfective agents that are active against all likely pathogens (ie, bacterial, viral, fungal)
    - Choice of specific agent(s) for empiric antimicrobial therapy depends on suspected source of infection, clinical situation, recent antibiotic use, and local resistance patterns [4]
    - Current Surviving Sepsis guideline recommends empiric combination therapy using at least 2 antibiotics from different classes for patients with septic shock [18]
    - Consult a clinical pharmacist if possible to optimize dosing and administration according to pharmacokinetic and pharmacodynamic principles (eg, continuous versus intermittent infusion of β-lactam agents) [18]
    - Empiric antibiotics should be de-escalated when culture and sensitivity results are available [17]
  - For suspected pneumonia [42]
    - Community-acquired pneumonia
      - Broad-spectrum β-lactam agent (cefotaxime, ceftazidime, cefepime, or piperacillin-tazobactam) plus either a respiratory fluoroquinolone (moxifloxacin or levofloxacin) or azithromycin
    - Medical care–associated pneumonia
      - Antipseudomonal carbapenem (imipenem, doripenem, or meropenem) or cefepime
      - If legionella is a possibility, add azithromycin or a fluoroquinolone [18]
    - For either community-acquired or medical care–associated pneumonia, add oseltamivir if suspected or confirmed influenza; IV peramivir can be used if oral or enteric oseltamivir cannot be tolerated [22, 43]
  - For suspected abdominal source [42]
    - Community-acquired infection
      - Carbapenem (imipenem, doripenem, or meropenem) or piperacillin-tazobactam with or without an aminoglycoside
      - For suspected biliary tract infection, piperacillin-tazobactam or ampicillin-sulbactam or ceftriaxone plus metronidazole
    - Medical care–associated infection
      - Antipseudomonal carbapenem (imipenem or meropenem) with or without an aminoglycoside
  - For suspected urinary source [42]
    - Community-acquired infection
      - Antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin)
        - If urine Gram stain shows gram-positive cocci, use either ampicillin or vancomycin, with or without an aminoglycoside
    - Medical care–associated infection
      - Vancomycin plus either imipenem or meropenem or cefepime
  - For suspected skin and soft tissue infection [42]
    - Community-acquired infection
      - Vancomycin or daptomycin plus either imipenem or meropenem or piperacillin-tazobactam

Published January 26, 2016; Updated December 17, 2019

        - Medical care–associated infection
            - Vancomycin or daptomycin plus either imipenem or meropenem or cefepime
        - For either community-acquired or medical care–associated infection
            - Add clindamycin if toxin-producing organism is suspected (eg, ***Streptococcus pyogenes***, ***Staphylococcus aureus***)
    - For unknown source in adults[42]
        - Community-acquired infection
            - Vancomycin plus a carbapenem (imipenem, doripenem, meropenem, or ertapenem)
        - Medical care–associated infection
            - Vancomycin plus cefepime
    - For unknown source in children[44]
        - Community-acquired infection
            - Third-generation cephalosporin (ceftriaxone or cefotaxime) plus vancomycin
        - Medical care–associated infection
            - Vancomycin plus either piperacillin-tazobactam, ceftazidime, cefepime, or a carbapenem (imipenem or meropenem)
    - Other considerations
        - Add oseltamivir if influenza is likely (IV peramivir can be used if oral or enteric oseltamivir cannot be tolerated)[43]
        - An echinocandin may be added in medical care–associated cases in which yeast is a possible pathogen (eg, cases involving indwelling vascular catheters, intra-abdominal infection, or neutropenia)[42]
        - Add fidaxomicin, or oral or enteral vancomycin (with or without IV metronidazole) if ***Clostridium difficile*** infection is a possibility[45]
- Provide vasopressor agents to target a mean arterial pressure of at least 65 mm Hg, if initial fluid resuscitation has not achieved that goal; a higher target (eg, 75 mm Hg or more) may be appropriate in patients with baseline hypertension[18]
    - Norepinephrine is first line therapy[18, 46, 47]
        - There is some evidence that early administration (within 2 hours of shock onset) of norepinephrine improves outcomes, and that every hour of delay results in an incremental increase in mortality[48]
    - Epinephrine and vasopressin may be added if necessary to achieve target mean arterial pressure[18]
    - Dopamine is a third line agent used only in patients meeting specific cardiac criteria[18]
- Consider inotropic therapy with dobutamine as an adjunct or alternative to vasopressor therapy in select cases with elevated cardiac filling pressures and low cardiac output suggestive of myocardial dysfunction or persistent clinical signs of hypoperfusion after adequate volume and mean arterial pressure have been achieved[18]
- Consider corticosteroid therapy with IV hydrocortisone if fluid resuscitation and vasopressor therapy do not restore hemodynamic stability[18]
    - Use of steroids may be reasonable, even though evidence for efficacy is not definitive[49, 50, 51]
- Source control within the first 12 hours if possible (eg, drainage of abscess, debridement of necrotic tissue, relief of ureteral obstruction, removal of infected device)[18]

- Additional treatment required after initial management in select cases of sepsis
    - Blood product administration
        - RBC transfusion if hemoglobin level is less than 7 g/dL after tissue hypoperfusion has been treated adequately[52, 18]
            - Evidence suggests that transfusion to higher levels does not confer an advantage in mortality or ischemic events[52, 53]
            - Acute hemorrhage, myocardial ischemia, or severe hypoxemia may necessitate a higher transfusion threshold[18]
        - Administer platelets prophylactically in septic patients with thrombocytopenia and increased risk for bleeding[18]
            - Less than 10,000 cells/mm³
            - Less than 20,000 cells/mm³ if there is a significant risk of bleeding
            - Less than 50,000 cells/mm³ for active bleeding, invasive procedure
    - Glycemic control targeting an upper blood glucose level of 180 mg/dL or less[18]
        - Evidence suggests that there is no benefit in tighter control and that adverse events are more frequent
    - Deep vein thrombosis prophylaxis using a combination of daily pharmacologic therapy and intermittent pneumatic compression devices[18]
    - Stress ulcer prophylaxis with a proton pump inhibitor or H_2 blocker is recommended for patients with sepsis or septic shock who are at risk for gastrointestinal bleeding[18]
    - Continuous renal replacement therapy or intermittent hemodialysis is recommended for acute kidney injury[18]
    - Oral nutrition or (if necessary) enteral nutrition within the first 48 hours after diagnosis, with low-dose feeding as tolerated[18]
        - If enteral feeding is not possible initially, a 7-day trial of IV glucose and advancement of enteral feeding is recommended over early parenteral nutrition

Published January 26, 2016; Updated December 17, 2019

- Once the causative pathogen is identified, de-escalate antimicrobial treatment, based on culture and sensitivity results, and continue for a duration appropriate to the diagnosis (7-10 days in most cases) [18]
  - De-escalation may be associated with improved survival [54]
  - Combination therapy is recommended in some circumstances: [18]
    - Ongoing septic shock
    - Multidrug-resistant pathogens such as ***Acinetobacter*** and ***Pseudomonas*** species
    - Bacteremic infections caused by ***Streptococcus pneumoniae*** (eg, β-lactam agent plus a macrolide)
    - Group A streptococcal toxic shock (penicillin and clindamycin)
  - Antimicrobial therapy may need to be continued past 7 to 10 days in certain clinical situations: [18]
    - Endocarditis
    - Immunologic deficiencies, such as neutropenia
    - Slow clinical response to antimicrobial therapy
    - Undrainable foci of infection
    - Bacteremia with ***Staphylococcus aureus***
    - Select fungal and viral infections
  - Shorter courses may be appropriate in patients with urinary tract or intra-abdominal infections and rapid clinical response to prompt source control [18]
    - Procalcitonin levels within reference range can be used to support a decision to discontinue antibiotics in these patients and in those who initially appeared septic but in whom no evidence for infection has emerged
- Drug therapy
  - Antimicrobial agents [4]
    - Broad-spectrum penicillins
      - Ampicillin-sulbactam
        - Ampicillin Sodium, Sulbactam Sodium Solution for injection; Infants†, Children†, and Adolescents†: 100 to 200 mg/kg/day ampicillin component (150 to 300 mg/kg/day ampicillin; sulbactam) IV divided every 6 hours (Max: 8 g/day ampicillin [12 g/day ampicillin; sulbactam]); use higher dose for serious or complicated infections. Doses up to 400 mg/kg/day ampicillin component (600 mg/kg/day ampicillin; sulbactam) have been reported rarely for serious infections.
          - Off-label use in pediatric age groups
        - Ampicillin Sodium, Sulbactam Sodium Solution for injection; Adults: 1.5 g (1 g ampicillin and 0.5 g sulbactam) or 3 g (2 g ampicillin and 1 g sulbactam) IV/IM every 6 hours.
      - Piperacillin-tazobactam [18]
        - Piperacillin Sodium, Tazobactam Sodium Solution for injection; Infants, Children, and Adolescents: 80 mg/kg/dose piperacillin component (90 mg/kg/dose piperacillin; tazobactam) IV every 6 hours (Max: 4 g/dose piperacillin [4.5 g/dose piperacillin; tazobactam]).
        - Piperacillin Sodium, Tazobactam Sodium Solution for injection; Adults: 3.375 g (3 g piperacillin and 0.375 g tazobactam) IV every 6 hours or 4.5 g (4 g piperacillin and 0.5 g tazobactam) IV every 6 to 8 hours for 7 to 10 days as part of combination therapy.
    - Cephalosporins
      - Third-generation [18]
        - Ceftriaxone
          - Ceftriaxone Sodium Solution for injection; Infants, Children, and Adolescents: 50 to 100 mg/kg/day IV/IM divided every 12 to 24 hours (Max: 4 g/day).
          - Ceftriaxone Sodium Solution for injection; Adults: 1 to 2 g IV/IM every 12 to 24 hours (Max: 4 g/day) depending on severity of illness and causative organism. For sepsis, start within 1 hour of recognition as part of empiric multi-drug therapy; generally treat 7 to 10 days depending upon patient response, site of infection, and pathogen(s). Deescalate when possible.
        - Ceftazidime
          - Antipseudomonal cephalosporin
          - Ceftazidime Sodium Solution for injection; Infants and Children: 30 to 50 mg/kg/dose IV every 8 hours (Max: 2 g/dose); use higher doses (e.g., 50 mg/kg/dose IV every 8 hours) for immunocompromised patients. 200 to 300 mg/kg/day IV divided every 8 hours (Max: 12 g/day) recommended by AAP for serious Pseudomonas infections.
          - Ceftazidime Sodium Solution for injection; Adolescents: 2 g IV every 8 hours.
          - Ceftazidime Sodium Solution for injection; Adults: 2 g IV every 8 hours. Start within 1 hour of recognition as part of empiric multi-drug therapy; generally treat 7 to 10 days depending upon patient response, site of infection, and pathogen(s). Deescalate when possible.

Published January 26, 2016; Updated December 17, 2019

- Fourth-generation [18]
  - Cefepime
    - Cefepime Hydrochloride Solution for injection; Adults: 1 to 2 g IV every 8 to 12 hours.
- Carbapenems [18]
  - Imipenem-cilastatin
    - Imipenem, Cilastatin Sodium Solution for injection; Infants 1 to 2 months weighing 1.5 kg or more: 25 mg/kg/dose IV every 6 hours.
    - Imipenem, Cilastatin Sodium Solution for injection; Infants 3 to 11 months, Children, and Adolescents: 15 to 25 mg/kg/dose IV every 6 hours (Max: 2 g/day for fully susceptible organisms; 4 g/day for moderately susceptible organisms).
    - Imipenem, Cilastatin Sodium Solution for injection; Adults: 500 mg IV every 6 hours or 1 g IV every 8 hours for fully susceptible organisms and 1 g IV every 6 hours for organisms with intermediate susceptibility. Treat for 7 to 10 days depending upon patient response, site of infection, and pathogen(s).
  - Meropenem
    - Meropenem Solution for injection; Adults: 1 g IV every 8 hours and 500 mg IV every 6 hours have shown clinical efficacy in hospitalized patients with a variety of infections. For sepsis, start within 1 hour of recognition as part of empiric multi-drug therapy; generally treat 7 to 10 days depending upon patient response, site of infection, and pathogen(s). Deescalate when possible.
- Levofloxacin [18]
  - Provides coverage of respiratory pathogens and gram-negative aerobic bacteria, including ***Pseudomonas aeruginosa***
  - Levofloxacin Solution for injection; Adults: 750 mg IV every 24 hours for at least 7 days.
- Azithromycin
  - Azithromycin Solution for injection; Adults: 500 mg IV once daily for at least 5 days.
- Aminoglycosides
  - Gentamicin (extended-interval dosing) [18]
    - Gentamicin Sulfate Solution for injection; Infants, Children, and Adolescents: 5 to 7.5 mg/kg/dose IV/IM every 24 hours.
    - Gentamicin Sulfate Solution for injection; Adults: 5 to 7 mg/kg/dose IV/IM. Dosing interval often determined via nomogram and adjusted based on a random concentration drawn 8 to 12 hours after the first dose; dosing intervals of 24, 36, and, in some cases, 48 to 72 hours, may be necessary. For sepsis, start within 1 hour of recognition as part of empiric multi-drug therapy; generally treat 7 to 10 days depending upon patient response, site of infection, and pathogen(s).
  - Amikacin
    - Enhanced antipseudomonal activity
    - Amikacin Sulfate Solution for injection; Adults: 15 to 20 mg/kg/dose IV/IM. Initial dose intervals are often determined using a nomogram, then adjusted based on random concentration drawn 8 to 12 hours after first dose; dosing intervals of 24, 36, and, in some cases, 48 to 72 hours, may be necessary. For sepsis, start within 1 hour of recognition as part of empiric multi-drug therapy; generally treat 7 to 10 days depending upon patient response, site of infection, and pathogen(s). Deescalate when possible.
- Vancomycin
  - Vancomycin Hydrochloride Solution for injection; Infants, Children, and Adolescents: 40 to 60 mg/kg/day IV divided every 6 hours; a loading dose of 20 to 25 mg/kg IV may be considered for seriously ill patients. Adjust dosage based on serum concentrations. For MRSA, treat at least 2 weeks for uncomplicated bacteremia and 4 to 6 weeks for complicated bacteremia.
  - Vancomycin Hydrochloride Solution for injection; Adults: 25 to 30 mg/kg (actual body weight) IV loading dose, then 15 to 20 mg/kg/dose (actual body weight) IV every 8 to 12 hours per guidelines. Adjust dose based on serum concentrations. FDA-approved dosage is 500 mg IV every 6 hours or 1 g IV every 12 hours. For MRSA, treat at least 2 weeks for uncomplicated bacteremia and 4 to 6 weeks for complicated bacteremia.

Published January 26, 2016; Updated December 17, 2019

- Oral vancomycin for ***Clostridium difficile*** infections:[45]
  - Vancomycin Hydrochloride Oral solution; Infants, Children, and Adolescents: 40 mg/kg/day (Max: 2 g/day) PO in 3 to 4 divided doses for 7 to 10 days is FDA-approved dosage. Clinical guidelines recommend 10 mg/kg/dose (Max: 125 mg/dose) PO 4 times daily for 10 days as first line option for nonsevere initial cases or for first recurrence. For severe/fulminant cases, 10 mg/kg/dose (Max: 500 mg/dose) PO 4 times daily for 10 days; consider adding IV metronidazole. For second/subsequent episodes, treat with vancomycin using a tapered and/or pulse regimen: 10 mg/kg/dose (Max: 125 mg/dose) PO 4 times daily for 10 to 14 days, then 10 mg/kg/dose (Max: 125 mg/dose) PO 2 times daily for 1 week, then 10 mg/kg/dose (Max: 125 mg/dose) PO once daily for 1 week, then 10 mg/kg/dose (Max: 125 mg/dose) PO every 2 to 3 days for 2 to 8 weeks. Additional option for second/subsequent episodes is 10 mg/kg/dose (Max: 500 mg/dose) PO 4 times daily for 10 days and then rifaximin for 20 days.
  - Vancomycin Hydrochloride Oral capsule; Adults: 125 mg PO 4 times daily for 10 days as first line option for nonsevere/severe initial cases and for first recurrence after metronidazole therapy. For fulminant cases, 500 mg PO or nasogastric tube 4 times daily with IV metronidazole; consider vancomycin retention enema for ileus. For first recurrence in patients initially treated with vancomycin or in second/subsequent episodes, treat with vancomycin using a tapered and/or pulse regimen: 125 mg PO 4 times daily for 10 to 14 days, then 125 mg PO 2 times daily for 1 week, then 125 mg PO once daily for 1 week, then 125 mg PO every 2 to 3 days for 2 to 8 weeks. Additional option for second/subsequent episodes is vancomycin 125 mg PO 4 times daily for 10 days followed by rifaximin for 20 days.

- Fidaxomicin
  - For ***Clostridium difficile*** infection:
    - Fidaxomicin Oral tablet; Adults: 200 mg PO twice daily for 10 days. Clinical guidelines recommend fidaxomicin as first line option for nonsevere/severe initial cases and for first recurrence after vancomycin therapy. Also option for second/subsequent episodes.

- Metronidazole
  - Metronidazole Solution for injection; Infants†, Children†, and Adolescents†: 30 to 40 mg/kg/day IV divided every 6 to 8 hours (Usual Max: 500 mg/dose; up to 4 g/day rarely for severe infections) for 4 to 7 days as part of broad-spectrum combination therapy.
    - Off-label use in pediatric age groups
  - Metronidazole Solution for injection; Adults: 500 mg IV every 8 to 12 hours or 1,500 mg IV every 24 hours 4 to 7 days as part of broad-spectrum combination therapy; alternately, FDA-labeled dose is 15 mg/kg IV once, then 7.5 mg/kg/dose IV every 6 hours (Max: 4 g/day).
  - For ***Clostridium difficile*** infection:
    - Oral
      - Metronidazole Oral tablet; Infants, Children, and Adolescents: 7.5 mg/kg/dose (Max: 500 mg/dose) PO every 6 to 8 hours for 10 days. Clinical guidelines recommend oral metronidazole as first line therapy option for nonsevere initial episodes or first recurrence.
      - Metronidazole Oral tablet; Adults: 500 mg PO 3 times daily for 10 days recommended by clinical guidelines as alternative for nonsevere initial cases. Avoid repeated or prolonged courses.
    - IV
      - Metronidazole Solution for injection; Infants, Children, and Adolescents: 7.5 mg/kg/dose (Max: 500 mg/dose) IV every 6 to 8 hours for 10 days. Clinical guidelines recommend intravenous metronidazole in combination with oral vancomycin for initial severe or fulminant cases.
      - Metronidazole Solution for injection; Adults: 500 mg IV every 8 hours in combination with oral and rectal vancomycin, particularly if ileus is present, recommended by clinical guidelines for fulminant cases.

- Clindamycin
  - Clindamycin Phosphate Solution for injection; Infants, Children, and Adolescents 13 to 16 years: 40 mg/kg/day IV/IM divided every 6 to 8 hours (Max: 2,700 mg/day).
  - Clindamycin Phosphate Solution for injection; Adolescents 17 years: 600 mg IV/IM every 6 to 12 hours to 900 mg IV every 8 to 12 hours; every 6 to 8 hour intervals most commonly used in pediatric practice.
  - Clindamycin Phosphate Solution for injection; Adults: 600 mg IV/IM every 6 to 12 hours to 900 mg IV every 8 to 12 hours.

- Antiviral agents
  - Oseltamivir
    - Oseltamivir Phosphate Oral suspension; Infants 1 to 8 months: 3 mg/kg/dose PO twice daily for 5 days.
    - Oseltamivir Phosphate Oral suspension; Infants 9 to 11 months: 3.5 mg/kg/dose PO twice daily for 5 days.
    - Oseltamivir Phosphate Oral suspension; Children weighing 15 kg or less: 30 mg PO twice daily for 5 days.
    - Oseltamivir Phosphate Oral suspension; Children weighing 16 to 23 kg: 45 mg PO twice daily for 5 days.
    - Oseltamivir Phosphate Oral suspension; Children weighing 24 to 40 kg: 60 mg PO twice daily for 5 days.

Published January 26, 2016; Updated December 17, 2019

- Oseltamivir Phosphate Oral suspension; Children and Adolescents weighing more than 40 kg: 75 mg PO twice daily for 5 days.
- Oseltamivir Phosphate Oral capsule; Adults: 75 mg PO twice daily for 5 days.

- Peramivir
  - Peramivir Solution for injection; Infants 30 to 90 days: 8 mg/kg/dose IV once daily for 5 days as alternative in patients who are unable to tolerate or absorb oseltamivir. Consider longer courses (e.g., 10 days) for severely ill hospitalized patients or immunosuppressed patients.
  - Peramivir Solution for injection; Infants 91 to 180 days: 10 mg/kg/dose IV once daily for 5 days as alternative in patients who are unable to tolerate or absorb oseltamivir. Consider longer courses (e.g., 10 days) for severely ill hospitalized patients or immunosuppressed patients.
  - Peramivir Solution for injection; Infants older than 180 days and Children up to 5 years: 10 to 12 mg/kg/dose IV once daily for 5 days as alternative in patients who are unable to tolerate or absorb oseltamivir. Consider longer courses (e.g., 10 days) for severely ill hospitalized patients or immunosuppressed patients.
  - Peramivir Solution for injection; Children 6 years and older and Adolescents: 10 mg/kg/dose IV once daily (Max: 600 mg/dose) for 5 days as alternative in patients who are unable to tolerate or absorb oseltamivir. Consider longer courses (e.g., 10 days) for severely ill hospitalized patients or immunosuppressed patients.
  - Peramivir Solution for injection; Adults: 600 mg IV once daily for 5 days as alternative in patients who are unable to tolerate or absorb oseltamivir. Consider longer courses (e.g., 10 days) for severely ill hospitalized patients or immunosuppressed patients.

- Antifungal agents
  - Caspofungin[18]
    - Caspofungin Solution for injection; Neonates† and Infants 1 to 2 months†: Very limited data available; other agents preferred (i.e., amphotericin B, fluconazole). 25 mg/m2/dose IV every 24 hours may provide comparable exposure to usual dose in adults. Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary; review drug interactions. Treat for 2 weeks after documented clearance from bloodstream and resolution of symptoms. For invasive candidiasis with metastatic focus, therapy will be longer and response-dependent.
      - Off-label use in first 2 months of life
    - Caspofungin Solution for injection; Infants 3 months and older, Children, and Adolescents: 70 mg/m2 IV (Max: 70 mg/dose) loading dose on day 1, followed by 50 mg/m2/dose IV (Max: 70 mg/dose) once daily; if response inadequate, may increase to 70 mg/m2/day (Max: 70 mg/dose). Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary; review drug interactions. Treat for 2 weeks after documented clearance from bloodstream and resolution of symptoms. For invasive candidiasis with metastatic focus, therapy will be longer and response-dependent.
    - Caspofungin Solution for injection; Adults: 70 mg IV loading dose on day 1, then 50 mg IV once daily. Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary; review drug interactions. Treat for 2 weeks after documented clearance from bloodstream and resolution of symptoms. For invasive candidiasis with metastatic focus, therapy will be longer and response-dependent.

- Vasopressors
  - Norepinephrine
    - First line therapy[18]
    - Norepinephrine Bitartrate Solution for injection; Infants†, Children†, and Adolescents†: 0.1 mcg/kg/minute IV initially, then titrate upward to attain hemodynamic goals (Usual Max: 2 mcg/kg/minute IV).
      - Off-label use in pediatric age groups
    - Norepinephrine Bitartrate Solution for injection; Adults: Initially, up to 8 to 12 mcg/minute, as an IV infusion. Infusions are typically initiated and titrated in increments of 0.02 mcg/kg/minute (or more in emergency cases). The usual maintenance dose is 2 to 4 mcg/minute. Patients with refractory shock may require dosages of 8 to 30 mcg/minute. One trial limited infusions to a maximum of 0.19 mcg/kg/minute, then added additional agents for the treatment of shock. Rule out hidden blood volume depletion if patient remains hypotensive. Septic shock clinical guidelines recommend as first-line vasopressor.
  - Epinephrine
    - First or second line therapy; may be added or used as an alternative to norepinephrine[18]
    - Epinephrine Hydrochloride Solution for injection; Neonates†, Infants†, Children†, and Adolescents†: 0.1 to 1 mcg/kg/minute continuous IV infusion. Titrate to desired effect; doses up to 5 mcg/kg/minute may be necessary in shock.
      - Off-label use in pediatric age groups

Published January 26, 2016; Updated December 17, 2019

- Epinephrine Hydrochloride Solution for injection; Adults: 0.05 to 2 mcg/kg/minute continuous IV infusion; titrate every 10 to 15 minutes in increments of 0.05 to 0.2 mcg/kg/minute to achieve desired blood pressure goal. Once hemodynamically stable, wean by decreasing infusion rate every 10 to 30 minutes to determine if patient can tolerate gradual withdrawal. Septic shock clinical guidelines recommend adding epinephrine to norepinephrine or potentially substituting for norepinephrine to achieve target MAP.

– Vasopressin
- Second or third line therapy; may be added to norepinephrine if necessary or used as salvage therapy[18]
- Vasopressin Solution for injection; Adults: 0.01 units/minute continuous IV infusion initially. Titrate by 0.005 units/minute every 10 to 15 minutes until target blood pressure reached. Max: 0.07 units/minute. After 8 hours without catecholamines, taper by 0.005 units/minute every hour as tolerated.

– Dopamine
- Third line agent used only in patients with bradycardia and/or a low risk of tachyarrhythmias[18]
- Dopamine Hydrochloride Solution for injection; Infants, Children, and Adolescents: 2 to 20 mcg/kg/minute IV is usual range; start low and titrate in 2.5 to 5 mcg/kg/minute increments.
- Dopamine Hydrochloride Solution for injection; Adults: Initially, 2 to 5 mcg/kg/minute continuous IV infusion. Titrate upward in 5 to 10 mcg/kg/minute increments to attain hemodynamic goals, generally up to 20 mcg/kg/minute IV. Max: 50 mcg/kg/minute IV.

- Inotropes
  - Dobutamine
    - May be considered as an adjunct or alternative to vasopressor therapy in select cases[18]
      - Elevated cardiac filling pressures and low cardiac output suggestive of myocardial dysfunction
      - Persistent clinical signs of hypoperfusion after adequate volume and mean arterial pressure have been achieved
    - Dobutamine Hydrochloride Solution for injection; Infants, Children, and Adolescents: Initially, 0.5 to 1 mcg/kg/minute continuous IV infusion then titrate every few minutes to response. Usual dose: 2 to 20 mcg/kg/minute. Same dosage may be administered IO during CPR if no IV access.
    - Dobutamine Hydrochloride Solution for injection; Adults: Initially, 0.5 to 1 mcg/kg/minute continuous IV infusion then titrate every few minutes to hemodynamic goals. Usual dose: 2 to 20 mcg/kg/minute. Doses more than 20 mcg/kg/minute may increase heart rate. Max: 40 mcg/kg/minute.
- Corticosteroids
  - Hydrocortisone
    - Continuous IV hydrocortisone if fluid resuscitation and vasopressor therapy do not restore hemodynamic stability[18]
    - Hydrocortisone Sodium Succinate Solution for injection; Adults: 200 mg/day IV continuous infusion if adequate fluid resuscitation and vasopressor therapy unable to restore hemodynamic stability. Taper dose once vasopressors no longer required. Do not administer in sepsis in absence of shock. ACTH stimulation test not recommended to identify patients who should receive hydrocortisone.

- Nondrug and supportive care
  - Procedures
    - Fluid resuscitation
      - Begin fluid resuscitation with an infusion of isotonic crystalloid solution within the first hour[17] to patients with hypotension or a lactate level of 4 mmol/L; the recommended goal is 30 mL/kg within 3 hours[17,18]
        - Some experts favor use of a balanced solution (eg, lactated Ringer solution, Hartmann solution) over normal saline when large volumes are needed[55,39]
      - Albumin may be needed in patients requiring large volumes of crystalloids[18]
      - Titrate initial and continued fluid administration based on physiologic parameters such as heart rate, blood pressure, respiratory rate, oxygen saturation, urine output, and (if invasive monitoring has been started) mean arterial pressure (goal is 65 mm Hg for most patients)[18]
        - Such clinical monitoring may be supplemented by bedside cardiac ultrasonography if available[36]
      - Normalization of lactate levels may be used as a guide, in addition to hemodynamic parameters[34,18]
      - Care must be taken not to administer too much fluid, especially if there is little hemodynamic response to initial fluids[56,55]
    - Respiratory support
      - Give supplemental oxygen initially to all patients with sepsis to achieve target oxygen saturation of 94%-98% in adults[15]
        - More intensive respiratory support is required if supplemental oxygen does not improve oxygenation
      - If necessary, use mechanical ventilation for sepsis-induced acute respiratory distress syndrome[18]
        - May be needed to improve oxygenation, protect airway, or prevent imminent respiratory failure

Published January 26, 2016; Updated December 17, 2019

- Target a tidal volume of 6 mL/kg of predicted body weight
- Target a plateau pressure of 30 cm H_2O or less
- Apply PEEP to avoid alveolar collapse at end expiration
- Use strategies of higher rather than lower levels of PEEP with moderate to severe acute respiratory distress syndrome
- Implement recruitment maneuvers with severe refractory hypoxemia (eg, CPAP) if needed
- Consider prone positioning in patients with a PaO_2/FiO_2 ratio of 100 mm Hg or less
- Risk reduction strategies to prevent development of ventilator-associated pneumonia include:[57]
  - Elevate head of bed to 30° to 45°
  - Selective oral and digestive decontamination
  - Oropharyngeal decontamination with oral chlorhexidine gluconate
- Establish weaning protocols for patients to undergo spontaneous breathing trials regularly to evaluate the ability to discontinue mechanical ventilation

- If possible, use noninvasive mask ventilation as an alternative to mechanical ventilation
- Use caution with sedation, analgesia, and neuromuscular blockade in mechanically ventilated patients[18]
  - Minimize continuous or intermittent sedation in mechanically ventilated patients
  - Avoid neuromuscular blockade in patients without sepsis-induced acute respiratory distress syndrome
  - Use a short course of neuromuscular blockade of not greater than 48 hours for patients with early sepsis-induced acute respiratory distress syndrome and a PaO_2/FiO_2 ratio less than 150 mm Hg

– Source control[18]
- Determine source of infection as quickly as possible, and begin intervention within 12 hours if possible
- Use the least invasive but adequately effective strategy for source control (eg, percutaneous versus open surgical technique)
- Depending on the source, strategies may include the following:
  - Drain abscess
  - Debride infected tissue and necrotic tissue
  - Remove infected device
    - Remove intravascular catheters that are suspected to be a source as soon as an alternate access is established

– Blood product administration[18]
- Blood products may be required after initial management in select cases
  - Transfuse RBCs if:
    - Hemoglobin level is less than 7 g/dL after tissue hypoperfusion has been treated adequately
      - Target hemoglobin level after transfusion is 7 to 9 g/dL for adults
      - Transfusion may be indicated at higher thresholds in patients with myocardial ischemia, hemorrhage, or severe hypoxemia
  - Administer platelets prophylactically if platelet count is:
    - 10,000 cells/mm^3 or fewer in the absence of bleeding
    - 20,000 cells/mm^3 or fewer with a significant risk of bleeding
    - 50,000 cells/mm^3 or fewer for active bleeding, surgery, or invasive procedures

– Glycemic control[18]
- Target an upper blood glucose level of 180 mg/dL or less
- Begin insulin dosing when 2 consecutive blood glucose level readings are greater than 180 mg/dL
- Adjust insulin dose based on repeated blood glucose level measurements every 1 to 2 hours until glucose values and insulin rates are stable, then monitor every 4 hours and adjust insulin dose as needed

– Deep vein thrombosis prophylaxis[18]
- Subcutaneous low-molecular-weight heparin daily is the recommended pharmacologic therapy
- For creatinine clearance less than 30 mL/minute, use dalteparin or unfractionated heparin
- For those with a contraindication to pharmacoprophylaxis, mechanical prophylactic treatment is recommended
- Combination of daily pharmacologic therapy and intermittent pneumatic compression devices may be used in patients who have no contraindications to either measure

– Stress ulcer prophylaxis[18]
- Recommended for patients at risk for bleeding, such as those with the following:
  - Thrombocytopenia
  - Multiorgan failure
  - Mechanical ventilation
- Proton pump inhibitors rather than H_2 blockers are preferred

Published January 26, 2016; Updated December 17, 2019

- Renal replacement therapy [18]
  - For patients with acute renal failure resulting from sepsis
    - Continuous renal replacement therapies and intermittent hemodialysis are equivalent in most patients
    - Use continuous therapies to facilitate management of fluid balance in hemodynamically unstable septic patients
- Nutrition [18]
  - Administer oral feedings or (if necessary) enteral feedings within the first 48 hours after diagnosis
  - Avoid mandatory full caloric feeding in the first week
    - Advance low-dose feeding only as tolerated
  - Avoid parenteral nutrition in the first week, even if enteral feeding is not possible initially; use IV glucose and attempt to advance enteral feeding
  - Consider prokinetic agents in patients with feeding intolerance
  - Consider a postpyloric feeding tube in patients with feeding intolerance who are at risk for aspiration
  - Use nutrition without specific immunomodulating supplementation

- Comorbidities
  - Common comorbidities include conditions that cause immunosuppression:
    - HIV infection [13, 12]
    - Hematologic malignancies [13]
    - Splenic deficiency [13]
    - Chronic conditions requiring high-dose corticosteroids or other immunosuppressant therapy [13]
    - Chronic renal failure [12]
    - Diabetes mellitus [12]
    - Excessive alcohol use [12]
- Special populations
  - Elderly people [7]
    - Elderly people are more likely to have repeated antimicrobial exposure due to chronic illness and medical intervention, resulting in multidrug-resistant microbial flora; very-broad-spectrum empirical antimicrobial therapy is required
    - Age-related renal and hepatic impairment put elderly people at higher risk for adverse events related to drug therapy; careful drug monitoring is necessary, and dose adjustment may be necessary
    - Increased capacitance of vasculature in elderly people creates a narrower therapeutic range of fluid resuscitation; there is a risk for either underresuscitation or fluid overload
  - Pediatric patients [58, 59, 19]
    - Assessment parameters are altered for pediatric patients
      - Vital signs and WBC counts are age dependent (tables are available [59])
      - Pediatric patients often have a lactate level within reference range in septic shock; do not exclude sepsis on the basis of lactate levels within reference range [19]
    - Young children are at greater risk for respiratory collapse than older children and adults [59]
      - Begin high-flow oxygen within the first few minutes
      - Avoid mechanical ventilation if less invasive means of respiratory support are adequate, owing to associated increased intrathoracic pressure, which can reduce venous return and worsen shock [19]
        - If mechanical ventilation is necessary, institute lung-protective strategies (eg, high-frequency oscillatory ventilation)
      - Extracorporeal membrane oxygenation is suggested for pediatric patients with refractory respiratory failure related to septic shock and/or refractory septic shock [19, 58]
    - Vascular access is more difficult in pediatric patients but may be aided by use of ultrasonography
      - Intraosseous route is an option for fluid resuscitation and delivery of antibiotics (preferably within 1 hour) and other medications [58]
      - As soon as access is obtained, administer isotonic crystalloids or albumin as bolus of up to 20 mL/kg over 5 to 10 minutes [58]
        - Repeat as needed, up to 60 mg/kg, aiming to restore age-appropriate blood pressure and heart rate, capillary refill (2 seconds or less), strong peripheral pulses, urine output (more than 1 mL/kg/hour), and mentation
        - A pump may be required to deliver such volume at the necessary rate
    - Vasopressors and inotropic agents may be required earlier in pediatric patients because of limited ability to increase heart rate beyond higher baseline rates typical in children [58]
      - Epinephrine is first line agent (0.05-0.3 mcg/kg/minute) instituted when hemodynamic parameters do not improve with 40 to 60 mL/kg fluids, or if signs of fluid overload preclude further fluid resuscitation

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- Further use of vasopressors and inotropes is determined by whether shock is characterized as warm or cold
  - Warm (bounding pulse, capillary refill time less than 1 second, skin flushed, ruddy): norepinephrine 0.05 mcg/kg and titrate to normalize parameters
  - Cold (weak pulse, capillary refill 3 seconds or longer, cool mottled skin): continue epinephrine; consider short-acting vasodilator such as nitroprusside or nitroglycerin if blood pressure is adequate
- Pediatric patients may be at higher risk for adrenal insufficiency with sepsis; when fluid resuscitation and catecholamines have failed to reverse shock, administration of hydrocortisone may be considered, preferably after obtaining blood specimen for cortisol level [58]
- Hypoglycemia and hypocalcemia are common in children with sepsis; the former may be an indicator of adrenal insufficiency [58]
- Pediatric patients are at increased risk for toxic shock; clindamycin (in addition to primary antistaphylococcal or antistreptococcal therapy) and antitoxin therapy (eg, IV immunoglobulin) are recommended for toxic shock syndrome with refractory hypotension [19]

MONITORING

- Monitor blood pressure, heart rate, mean arterial pressure (for patients with shock), and urine output continuously during fluid resuscitation
- Monitor serum lactate levels every 2 hours to guide fluid resuscitation
- Serum procalcitonin, although not considered to be diagnostic for sepsis, may be followed as a way to determine when antibiotics may be safely discontinued

COMPLICATIONS AND PROGNOSIS

COMPLICATIONS

- Ventilator-associated pneumonia [18]
- End-organ dysfunction (eg, renal, pulmonary) [19]
- Deep vein thrombosis [18]
- Stress ulcer [18]
- Physical, cognitive, and emotional disabilities [4]

PROGNOSIS

- Mortality rate varies depending on response to treatment and severity at presentation [4, 60]
- With sepsis now defined as including organ failure (since 2016), [1] the portion of the evidence base from before 2016 that is most relevant is the portion reporting on the categories of "severe sepsis and septic shock" (as then defined) [61, 60]
- Under those definitions, some representative reports gave mortality ranges as follows:
  - Severe sepsis: 25% to 30% [4, 13]
  - Septic shock: 40% to 70% [13, 4]
    - In septic shock, mortality increases by 7.6% for every hour that appropriate antimicrobial medications are delayed [2]
- Patients who survive sepsis have a higher mortality rate after discharge as well as higher incidences of persistent pulmonary dysfunction, physical disability, cognitive dysfunction, and posttraumatic stress disorder [4]

SCREENING AND PREVENTION

SCREENING

PREVENTION

- Prevention of community-acquired infection
  - Vaccination
    - Annual influenza vaccine for all persons older than 6 months [62, 63]
    - Age-appropriate vaccines for children and adolescents [62]
    - Pneumococcal vaccines for older adults (23-valent pneumococcal polysaccharide vaccine for everyone aged 65 years or older; it may be preceded by 13-valent pneumococcal conjugate vaccine as individualized by shared decision making) [64, 63]
    - Other vaccines (eg, meningococcus, ***Haemophilus*** species) as recommended for chronic conditions or immunodeficiency [63, 62]
  - Wound care
  - Personal hygiene
- Prevention of medical care–associated infection [65]
  - Proper hand hygiene and general infection control measures
  - Oral care and positioning to prevent hospital-acquired pneumonia and ventilator-associated pneumonia
  - Care and timely removal of indwelling devices (eg, urinary catheters, IV access)
  - Wound and surgical site care

Published January 26, 2016; Updated December 17, 2019

SYNOPSIS

KEY POINTS

- Sepsis is a life-threatening systemic syndrome caused by a microbial infection and dysregulated physiologic response
  - Pathogen invasion prompts proinflammatory and subsequent antiinflammatory mediators. This response can lead to the cascade effect of sepsis, including endothelial damage, vascular permeability, microvascular dysfunction, and coagulopathies, which, if not treated promptly and adequately, can lead to organ system failure and death
- Presentation is variable, depending on source of infection, but it often includes fever, tachypnea, tachycardia, hypotension, and signs of tissue hypoperfusion
- Diagnosis is based on history, clinical presentation, leukocytosis or leukopenia, and lactate level; blood and other cultures are useful in determining the pathogen responsible; imaging may be done as an adjunct to identify the source of sepsis
- Treatment includes immediate stabilization, fluid resuscitation, collection of blood and other relevant cultures, and initiation of antimicrobials, hemodynamic support, and source control; treatment should proceed rapidly (within 1 hour [17]), regardless of setting
- Complications include ventilator-associated pneumonia, end-organ dysfunction, deep vein thrombosis, stress ulcers, and long-term disability
- Prognosis depends on early identification and treatment, response to treatment, and severity at presentation
  - Sepsis has a mortality rate of 25% to 30% [4, 13]
  - Septic shock has a mortality rate of 40% to 70% [4, 13]

URGENT ACTION

- Initial treatment should proceed rapidly, regardless of setting; it should focus on respiratory and circulatory support and prompt administration of antimicrobial therapy [18]
- In septic shock, the risk of death increases every hour that appropriate antimicrobial medications are delayed; it is imperative to start treatment upon recognition [4]
- Early lactate measurement is key to recognizing sepsis; delay is associated with increased mortality [66]
- Surviving Sepsis Campaign bundle (2018) recommended doing the following within the first hour when diagnosis is suspected: [17]
  - Measure lactate level
  - Take blood culture specimens
  - Administer broad-spectrum antibiotics
  - For patients with hypotension or lactate levels of 4 mmol/L or higher:
    - Administer isotonic crystalloid fluids (30 mL/kg)
    - If hypotension occurs or persists during or after fluid resuscitation, add vasopressors

PITFALLS

- Signs and symptoms of sepsis are highly variable, and hypoperfusion may be subtle in healthy adults; maintain a high degree of suspicion, because prompt identification and treatment are crucial to recovery [13]
- Presentation of sepsis in elderly people is often different from presentation in younger people, which may delay diagnosis and treatment [7]
  - Be aware of subtle signs of sepsis in elderly people, such as delirium, urinary incontinence, weakness, malaise, anorexia, and falls
  - Elderly patients are less likely to present with fever, tachycardia, and hypoxemia than younger patients

SELECTED REFERENCES

1 Singer M et al: The Third International Consensus Definitions for sepsis and septic shock (Sepsis-3). JAMA. 315(8):801-10, 2016
2 Perman SM et al: Initial emergency department diagnosis and management of adult patients with severe sepsis and septic shock. Scand J Trauma Resusc Emerg Med. 20:41, 2012
3 Worapratya P et al: Septic shock in the ER: diagnostic and management challenges. Open Access Emerg Med. 11:77-86, 2019
4 Gauer RL: Early recognition and management of sepsis in adults: the first six hours. Am Fam Physician. 88(1):44-53, 2013
5 Novosad SA et al: Vital signs: epidemiology of sepsis: prevalence of health care factors and opportunities for prevention. MMWR Morb Mortal Wkly Rep. 65(33):864-9, 2016
6 Tunkel AR: Subdural empyema, epidural abscess, and suppurative intracranial thrombophlebitis. In: Bennett JE et al, eds: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, Updated Edition. 8th ed. Philadelphia, PA: Saunders; 2015:1177-85
7 Girard TD et al: Insights into severe sepsis in older patients: from epidemiology to evidence-based management. Clin Infect Dis. 40(5):719-27, 2005
8 Elixhauser A et al: Septicemia in U.S. Hospitals, 2009. HCUP Statistical Brief No. 122. Healthcare Cost and Utilization Project website. Published October 2011. Accessed December 10, 2019. https://www.hcup-us.ahrq.gov/reports/statbriefs/sb122.pdf
9 Hall MJ et al: Inpatient Care for Septicemia or Sepsis: A Challenge for Patients and Hospitals. NCHS Data Brief No. 62. National Center for Health Statistics website. Published June 2011. Accessed December 10, 2019. https://www.cdc.gov/nchs/data/databriefs/db62.pdf
10 Kermorvant-Duchemin E et al: Outcome and prognostic factors in neonates with septic shock. Pediatr Crit Care Med. 9(2):186-91, 2008
11 Watson RS et al: The epidemiology of severe sepsis in children in the United States. Am J Respir Crit Care Med. 167(5):695-701, 2003
12 Esper AM et al: The role of infection and comorbidity: factors that influence disparities in sepsis. Crit Care Med. 34(10):2576-82, 2006
13 Lever A et al: Sepsis: definition, epidemiology, and diagnosis. BMJ. 335(7625):879-83, 2007
14 Barnato AE et al: Racial variation in the incidence, care, and outcomes of severe sepsis: analysis of population, patient, and hospital characteristics. Am J Respir Crit Care Med. 177(3):279-84, 2008
15 National Institute for Health and Care Excellence: Sepsis: Recognition, Diagnosis and Early Management. NICE guideline NG51. Updated April 2019. Accessed December 9, 2019. https://www.nice.org.uk/guidance/ng51/chapter/Update-information

Published January 26, 2016; Updated December 17, 2019

16 Singer M et al: qSOFA, cue confusion. Ann Intern Med. 168(4):293-5, 2018
17 Levy MM et al: The Surviving Sepsis Campaign Bundle: 2018 Update. Crit Care Med. 46(6):997-1000, 2018
18 Rhodes A et al: Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 43(3):304-77, 2017
19 Dellinger RP et al: Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 41(2):580-637, 2013
20 Long B et al: Ready for prime time? Biomarkers in sepsis. Emerg Med Clin North Am. 35(1):109-22, 2017
21 Andriolo BN et al: Effectiveness and safety of procalcitonin evaluation for reducing mortality in adults with sepsis, severe sepsis or septic shock. Cochrane Database Syst Rev. 1:CD010959, 2017
22 Metlay JP et al: Diagnosis and treatment of adults with community-acquired pneumonia: an official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 200(7):e45-67, 2019
23 Creamer A et al: Imaging in severe sepsis and septic shock: is early radiological identification of occult sources of infection needed? Crit Care. 18(suppl 2):P12, 2014
24 van der Hulle T et al: Recent developments in the diagnosis and treatment of pulmonary embolism. J Intern Med. 279(1):16-29, 2016
25 Jones MR et al: Drug-induced acute pancreatitis: a review. Ochsner J. 15(1):45-51, 2015
26 Gosmanov AR et al: Hyperglycemic crises: diabetic ketoacidosis (DKA), and hyperglycemic hyperosmolar state (HHS). In: De Groot LJ et al, eds: Endotext [internet]. South Dartmouth, MA: MDText.com; 2015
27 Rushworth RL et al: A descriptive study of adrenal crises in adults with adrenal insufficiency: increased risk with age and in those with bacterial infections. BMC Endocr Disord. 14:79, 2014
28 Bennardello F et al: The prevention of adverse reactions to transfusions in patients with haemoglobinopathies: a proposed algorithm. Blood Transfus. 11(3):377-84, 2013
29 Nates JL et al: ICU admission, discharge, and triage guidelines: a framework to enhance clinical operations, development of institutional policies, and further research. Crit Care Med. 44(8):1553-602, 2016
30 Afshar M et al: Patient outcomes and cost-effectiveness of a sepsis care quality improvement program in a health system. Crit Care Med. 47(10):1371-9, 2019
31 PRISM Investigators et al: Early, goal-directed therapy for septic shock--a patient-level meta-analysis. N Engl J Med. 376(23):2223-34, 2017
32 Yu H et al: Effect of early goal-directed therapy on mortality in patients with severe sepsis or septic shock: a meta-analysis of randomised controlled trials. BMJ Open. 6(3):e008330, 2016
33 Coccolini F et al: Early goal-directed treatment versus standard care in management of early septic shock: meta-analysis of randomized trials. J Trauma Acute Care Surg. 81(5):971-8, 2016
34 Hernández G et al: Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock: the ANDROMEDA-SHOCK randomized clinical trial. JAMA. 321(7):654-64, 2019
35 Gattinoni L et al: Understanding lactatemia in human sepsis: potential impact for early management. Am J Respir Crit Care Med. 200(5):582-9, 2019
36 Levitov A et al: Guidelines for the appropriate use of bedside general and cardiac ultrasonography in the evaluation of critically ill patients--part II: cardiac ultrasonography. Crit Care Med. 44(6):1206-27, 2016
37 Jiang L et al: Albumin versus other fluids for fluid resuscitation in patients with sepsis: a meta-analysis. PLoS One. 9(12):e114666, 2014
38 Rochwerg B et al: Fluid resuscitation in sepsis: a systematic review and network meta-analysis. Ann Intern Med. 161(5):347-55, 2014
39 Semler MW et al: Balanced crystalloid solutions. Am J Respir Crit Care Med. 199(8):952-60, 2019
40 Peltan ID et al: ED door-to-antibiotic time and long-term mortality in sepsis. Chest. 155(5):938-46, 2019
41 Johnston AN et al: Effect of immediate administration of antibiotics in patients with sepsis in tertiary care: a systematic review and meta-analysis. Clin Ther. 39(1):190-202.e6, 2017
42 Munford RS et al: Sepsis, severe sepsis, and septic shock. In: Bennett JE et al, eds: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, Updated Edition. 8th ed. Philadelphia, PA: Saunders; 2015:914-34
43 CDC: Influenza Antiviral Medications: Summary for Clinicians. CDC website. Updated November 29, 2019. Accessed December 10, 2019. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm
44 Guzman-Cottrill JA et al: The systemic inflammatory response syndrome (SIRS), sepsis, and septic shock. In: Long SS et al, eds: Principles and Practice of Pediatric Infectious Diseases. 5th ed. Philadelphia, PA: Saunders; 2018:98-102
45 McDonald LC et al: Clinical practice guidelines for Clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 66(7):e1-48, 2018
46 Avni T et al: Vasopressors for the treatment of septic shock: systematic review and meta-analysis. PLoS One. 10(8):e0129305, 2015
47 Zhou F et al: Vasopressors in septic shock: a systematic review and network meta-analysis. Ther Clin Risk Manag. 11:1047-59, 2015
48 Bai X et al: Early versus delayed administration of norepinephrine in patients with septic shock. Crit Care. 18(5):532, 2014
49 Rochwerg B et al: Corticosteroids in sepsis: an updated systematic review and meta-analysis. Crit Care Med. ePub, 2018
50 Lamontagne F et al: Corticosteroid therapy for sepsis: a clinical practice guideline. BMJ. 362:k3284, 2018
51 Volbeda M et al: Glucocorticosteroids for sepsis: systematic review with meta-analysis and trial sequential analysis. Intensive Care Med. 41(7):1220-34, 2015
52 Holst LB et al: Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med. 371(15):1381-91, 2014
53 Rygård SL et al: Higher vs. lower haemoglobin threshold for transfusion in septic shock: subgroup analyses of the TRISS trial. Acta Anaesthesiol Scand. 61(2):166-75, 2017
54 Paul M et al: Antibiotic de-escalation for bloodstream infections and pneumonia: systematic review and meta-analysis. Clin Microbiol Infect. 22(12):960-7, 2016
55 Loflin R et al: Fluid resuscitation in severe sepsis. Emerg Med Clin North Am. 35(1):59-74, 2017
56 Self WH et al: Liberal versus restrictive intravenous fluid therapy for early septic shock: rationale for a randomized trial. Ann Emerg Med. 72(4):457-66, 2018
57 Klompas M et al: Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol. 35(8):915-36, 2014
58 Davis AL et al: American College of Critical Care Medicine clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock. Crit Care Med. 45(6):1061-93, 2017
59 Prusakowski MK et al: Pediatric sepsis. Emerg Med Clin North Am. 35(1):123-38, 2017
60 Luhr R et al: Trends in sepsis mortality over time in randomised sepsis trials: a systematic literature review and meta-analysis of mortality in the control arm, 2002-2016. Crit Care. 23(1):241, 2019
61 Hajj J et al: The "centrality of sepsis": a review on incidence, mortality, and cost of care. Healthcare (Basel). 6(3), 2018
62 CDC: Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger, United States, 2020. CDC website. Updated February 3, 2020. Reviewed February 3, 2020. Accessed February 20, 2020. https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html
63 CDC: Recommended Adult Immunization Schedule for Ages 19 Years or Older, United States, 2020. CDC website. Updated February 3, 2020. Reviewed February 3, 2020. Accessed February 20, 2020. https://www.cdc.gov/vaccines/schedules/hcp/adult.html
64 Matanock A et al: Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: updated recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. 68(46):1069-75, 2019
65 Kleinpell RM et al: Targeting health care–associated infections: evidence-based strategies. In: Hughes RG, ed: Patient Safety and Quality: An Evidence-Based Handbook for Nurses. Rockville, MD: Agency for Healthcare Research and Quality; 2008
66 Han X et al: Implications of Centers for Medicare and Medicaid Services Severe Sepsis and Septic Shock Early Management Bundle and initial lactate measurement on the management of sepsis. Chest. ePub, 2018

Published January 26, 2016; Updated December 17, 2019