Screencast

Read the articles at the end of this document---

Optional (for those of you going deeper in medicine)---Nice to know for EMT but don’t spend a lot of time on this:

- A carrier is a host (functioning as a reservoir) that contains the pathogen and can pass it on (is contagious) but may not be symptomatic. A vector is an organism that can pass on the pathogen but who is not infected itself (mosquito for example).

- Mucous membranes (secreting mucus) and the skin form a barrier. Stomach acid acts as a barrier by destroying some bacteria. Other bacteria (“good”) compete with pathogenic bacteria for a limited nutrient supply and thereby form something of a barrier.

Autoimmune response

- Systemic lupus erythmatosus (“Lupus”)—painful joints with swelling although facial “butterfly” rash is most noticeable but may have kidney, aortic or vascular complications
- Rheumatoid arthritis—painful deterioration of joints

Patients at risk—

- Pulmonary system mucus is cleared by the cilia that move the mucus toward the pharynx where it can be coughed up. Patients with damaged cilia or reduced mucus production (natural impact of aging) and those who are not able to be upright to take advantage of the naturally intended posture, are at risk for pooling mucus / phlegm and the resulting infection (pneumonia). Older age patients may have stiffer lungs and weaker diaphragms adding to the problem.

- Bedridden patients do not get the advantage of gravity to naturally drain their kidneys and may have indwelling catheters that add to the infection risk.

- Bedridden patients may develop bed sores due to pressure that reduces circulation or complicated by naturally thinner skin and poor circulation related to aging.
• Each pathogen has a different incubation period (time from exposure until symptomatic). Often, the first symptoms are non-specific such as loss of appetite, fever, aches, headache.

• Communicable period—varies by pathogen with some being communicable from the first exposure while others are only communicable at certain times whether or not the patient is symptomatic. Symptomatic does NOT equal contagious.

▼ Inflammation—triggered by mast cells that are part of the immune system’s attempt to surround, eat and kill the pathogen; histamine and heparin release causes vasodilation and leaky capillaries (causing edema); fever, pain, swelling, redness

• Purulence (yellow-tinged white pus)—forms on skin or within the body in an abscess (cavity filled with pus) or within a cavity such as the pleural space (called an empyema)

▼ Some pathogens:
• RSV (Respiratory Syncytial Virus)—most at risk are infants (<1 year old); starts with common cold symptoms (cough, low-grade fever, runny nose) but it progresses to bronchiolitis (wheezing). Peak in late fall to early winter. Droplet spread but pathogen dies outside the body quickly and is easily killed with soap and water and standard cleaning of surfaces.

• Influenza—viral infection that tends to be seasonal (fall and winter) and is spread by droplets; signs are fever / aches / fatigue but may extend to sore throat / coughing if it settles in the respiratory tract (common) and that may progress to pneumonia or croup; flu may also include nausea-vomiting-diarrhea.

▼ Haemophilus Influenza—NOT the same as influenza; bacterial infection; respiratory infection that may spread to joints, meninges, pericardium as well as alveoli and pleura—pathogen may be present but the body can defend against it unless weakened by another disease (like flu):
• Plague—spread by fleas or rats; starts with headache / fatigue and hemoptysis (coughing up blood)

• Tuberculosis—respiratory infection that results in nodules forming in the lungs and that may lie dormant for years until the host is weakened for some reason; simple skin testing (PPD or Mantoux test); dry / hacking
cough with hemoptysis; a variant is multi-drug resistant (MDR-TB) that does not respond to the usual treatments of rifampin and isoniazid

• Croup—technically laryngotracheobronchitis; more common in peds 3 months to 3 years old in the fall; starts in throat but progresses to lungs; barking cough and difficulty breathing and stridor; humidified air (from shower) helps but may need beta-2 agonists
• Epiglottitis—focused infection of the epiglottis that is caused by both bacterial and viral pathogens; starts as sore throat / fever / voice changes but progresses to respiratory distress (on inspiration mostly) and drooling followed by high fever and stridor; humidified air helps but caution with limited airway manipulation or stimulation of the patient—prep for crash airway that may include needle cric

• Pertussis—looks like common cold at the onset but progresses to whooping cough and may have inspiratory wheeze; airborne transmission (very contagious)

▼ Gastroenteritis—several pathogens can lead to nausea-vomiting-diarrhea, loss of appetite and low-grade fever; management is based on dealing with hydration and treatment of nausea and fever when possible
  • C-dif—technically, clostridium difficile—typically caused by destruction of “good” bacteria by antibiotics leaving the C.dif unchecked—leading to persistent diarrhea with its risk for dehydration or electrolyte imbalances; particularly foul-smelling diarrhea; patient may be known to have
  • Salmonella—fever / chills / nausea-vomiting-diarrhea; bacterial pathogen transmitted via food
  • E.coli—the pathogenic version is bacterial and comes from contaminated water usually; produces cramping and nausea-vomiting-diarrhea
  • Food poisoning—improper cooking or contaminated food; bacterial that may start with heartburn and then progress to produce nausea-vomiting-diarrhea (may be bloody)

▼ Hepatitis
  • A—viral; presents with flu-like symptoms and may progress over time to full hepatitis signs
  • B—viral; presents with hepatitis symptoms
  • C—viral; mild symptoms that progresses to full liver failure
  • D—viral co-infection with some Hepatitis B

• MRSA—technically multiple-resistant staphylococcus aureus; transmitted by body fluids
SIRS—technically systemic inflammatory response syndrome that comes from prolonged and serious infection to where the immune system’s response feeds back on itself and produces high levels of cytokines; criteria for SIRS includes tachycardia, tachypnea, low EtCO2 and altered body temp (either above 38°C or below 36°C plus elevated WBC on blood work)
- third spacing results in hypovolemia from leaky capillaries
- may develop DIC where both inappropriate micro-clotting occurs along with bleeding
- may involve ARDS (acute respiratory distress syndrome)

Rash—may have skin vesicles that could open up and release infectious fluids
- Measles (Rubeola), Mumps, Rubella, Roseola and Chickenpox all present as a rash and are contagious via airborne droplets or contact with items that came in contact with droplets and that have not been decontaminated; some by other body fluids
- Lice—technically pediculosis may appear in various areas of the body as black specks or white pearls
- Scabies—appears as a rash from mites that burrow under the skin
- Syphilis—genital rash that may spread to hands if untreated and may have fever / fatigue / swollen lymph glands—and may progress to a dementia-like condition known as neurosyphilis with headaches, cranial nerve issues and signs of meningitis (stiff neck)

Sexually transmitted diseases:
- Gonorrhea—foul-smelling purulent (pus) discharge from genitals associated with difficult or painful urination; may spread to mouth or eyes or progress to pelvic inflammatory disease (PID)
- Chlamydia—urinary symptoms with or without pain; very common condition
- HIV—technically human immunodeficiency virus—sexually transmitted in many cases or shared needles; may present as flu-like illness with fever, fatigue, aches, rash, headache, night sweats; second stage is contagious by asymptomatic and may last many years; third stage is AIDS (acquired immune deficiency syndrome) which results in frequent infections including pnemocystis and tuberculosis along with various others—also complicated by diseases resulting from treatments of other conditions with antibiotics
Case Study

It is a beautiful Sunday afternoon when you and your partner are dispatched to the residence of a 78-year-old female, Mrs. Smith, who has experienced a change in mental status. Upon your arrival, you make contact with Mrs. Smith’s daughter who leads you to her mother. The daughter tells you that her mother has been recently treated for a urinary tract infection and seemed to be getting better. She tells you that over the last 12 hours her mother has had a noticeable change in alertness and is just not “acting right.”

You find Mrs. Smith lying in bed with her eyes open, but she does not make eye contact with you as you enter the room. Mrs. Smith is conscious, but lethargic and disoriented. Her airway is intact and she appears to be breathing without difficulty. Her blood pressure is 78/42, heart rate is 118, and respiratory rate is 26. Her skin is cool, pale, and diaphoretic with a room oxygen saturation of 91%. Mrs. Smith’s EtCO2 is 21 mmHg. She is afebrile. Your neurological exam reveals no focal deficits. Mrs. Smith weighs approximately 53 kg.

Your differential diagnosis includes hypo/hyperglycemia, dehydration, stroke/TIA, UTI, sepsis, and septic shock. Considering the patient’s medical history, recent health complaint, and physical exam findings, you conclude that septic shock is at the top of the differential.

The incidence of severe sepsis and septic shock is increasing in the elderly population. The elderly are at risk for sepsis due to comorbidities, multiple and prolonged hospitalizations, impaired immunity, the effects of aging, and functional limitations. Prehospital professionals must maintain a high level of suspicion to diagnose sepsis in the aging population as the initial clinical presentation may be ambiguous. The focus of this article is review the impact of sepsis on the aging population, causes, signs and symptoms, and management.

Background and Significance

Sepsis is defined as a syndrome characterized by an overwhelming systemic response of the body to an infection. It is common, expensive, and lethal! Severe sepsis and septic shock combined are the 10th leading cause of death, resulting in 215,000 deaths annually and is among one of the leaders of mortality and morbidity worldwide. There are an estimated 751,000 reported cases of sepsis every year with an annual cost of $16 billion. The mortality rate for the severely septic patients is about 15%-20%. Severe sepsis in children has a 10% mortality rate. Outcome data and evidence-based medicine clearly shows that because of better screening and early goal directed therapies of the septic patient, there is a reduction in mortality, despite an overall increase in the number of septic patients.

Causes and Diagnosis of Sepsis

Bacterial infections are the most common cause of sepsis. Respiratory tract infections are the most frequent cause of infection and accounts for 25% of all patients with sepsis. UTI’s are the second most frequent cause of infection also accounting for an additional 25% of all patients with sepsis. Sepsis can also be caused by other infections as well. Septic shock usually starts with a localized infection that develops into a widespread systemic inflammatory response. This is also known as Systemic Inflammatory Response Syndrome (SIRS). SIRS can also be caused by other factors than infection. Major trauma is among one of the highest causative factors for SIRS.

The human body is exposed to infectious organisms
Sepsis

arises when the body’s response to an infection injures its own tissues and organs. It may lead to shock, multiple organ failure, and death, especially if not recognized early and treated promptly.

From a local infection to a general inflammation

A local infection — e.g. in the lung — overcomes the body’s local defense mechanisms. Pathogenic germs and the toxins they produce leave the original site of the infection and enter the circulatory system.

Organ dysfunction

This leads to a general inflammatory response: SIRS (systemic inflammatory response syndrome). The function of individual organs starts to deteriorate and may completely fail. Sepsis starts with the onset of at least one new organ dysfunction.

Septic Shock

Several organs stop functioning sequentially or simultaneously, and cardio-circulatory failure leads to a sudden drop in blood pressure. This is called septic shock.

Sepsis is diagnosed when the patient has organ dysfunction and septic shock with the presence of hypotension. Signs and symptoms of sepsis and severe sepsis include fever or hypothermia, tachycardia, tachypnea, altered mental status, pain, warm or cold skin, and elevated PCO2. Signs and symptoms of septic shock include hypoperfusion, hypotension, oliguria, altered mental status, and metabolic acidosis.2,4,9

Because of impaired tissue oxygenation at the cellular level in severe sepsis and in septic shock, hyperlactatemia is typically present. Lactate is considered a marker of anaerobic metabolism. The role of raised blood lactate levels as a prognostic value is well documented. Normal lactate levels range from 0.5 to 1 mmol/L. According to the Surviving Sepsis Campaign, all patients with elevated lactate >4 mmol/L should begin early goal directed therapy regardless of blood pressure.2,10

Early recognition and early management are vital for the septic patient. Early goal directed therapy has shown a significant reduction in mortality rates. The primary goal of treating the sepsis patient is to maintain organ perfusion and improving tissue oxygenation. Key components of treatment include fluid administration, appropriate cultures prior to antibiotic administration, early targeted antibiotics and source control, and the use of vasopressors/inotropes when the fluid resuscitation optimized.2,4,11

SIRS criteria

SIRS is suspected when 2 or more of the following exist:

- Fever >38 C or <36 C
- Heart Rate >90 beats per minute
- Respiratory rate >20 breaths per minute or PaCO2 <32 mmHg
- Abnormal white blood cell count

Surviving Sepsis Campaign

The Surviving Sepsis Campaign established goal directed therapy bundles, which were updated this past April 2015. The Surviving Sepsis Campaign recommends for the treatment of severe sepsis and septic shock:

To be completed within 3 hours of time of presentation:
• Measure lactate level
• Obtain blood cultures prior to administration of antibiotics.
• Administer broad spectrum antibiotics.
• Administer 30ml/kg crystalloid for hypotension or lactate ≥4 mmol/L

To be completed within 6 hours of time of presentation:
• Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65 mmHg.
• In the event of persistent hypotension after initial fluid administration (MAP <65 mmHg) or if initial lactate was ≥4 mmol/L, re-assess volume status and tissue perfusion, and
• Re-measure lactate if initial lactate is elevated.¹¹

EMS Integration into a System of Care

EMS agencies have partnered with hospitals to jump start treatment based on EMS assessment and early notification. EMS agencies are now “alerting” hospitals for STEMI, stroke, and trauma patients. This early activation by EMS has improved outcomes for these types of patients and has been established as a best practice. A few EMS agencies have added one more early notification alert to their protocols, the “sepsis alert.” One recommendation for the activation of a sepsis alert is a suspected infection with a systolic blood pressure <90 mmHg OR two or more of the following criteria:

1. Heart rate >90 bpm;
2. Temperature <96.8 degrees F or >100 degrees F;
3. Respiratory rate >20 bpm
4. Acute altered mental status; or
5. Increased serum lactate levels (>4 mmol/L) or EtCO₂ ≤25 mmHg.º

In some EMS agencies, prehospital diagnostic tools for the assessment of the suspect sepsis patient include the use of point of care testing (POCT) lactic acid meters, and EtCO₂ measured with capnography. ⁹ In patients with ≥ 2 SIRS criteria (Figure x), an EtCO₂ measurement of ≤ 25 mmHg is strongly correlated with lactate levels > 4mmol/L.¹²

Impact

Returning to Mrs. Smith, you begin your treatment and prepare for transport. Your treatment will be guided by an approved sepsis protocol. Because Mrs. Smith meets four of the five criteria above, you enact a sepsis alert by radio to the receiving emergency department. You place Mrs. Smith on oxygen at high flow and establish vascular access with normal saline. You begin to administer 30 ml/kg bolus of normal saline. You place her on the cardiac monitor and obtain a 12 lead. You note blood glucose is 112 mg/dL. You place her on a cot and transport her to a specialty care facility. Mrs. Smith is admitted to the ICU with a higher chance of an improved outcome thanks to the collaborative effort of EMS and hospital, and the use of a “sepsis alert.”

About the Author

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References

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The immune system is a complex yet essential system that constitutes our body's infection defense. One of this system's unique abilities is its constant adaptation and modification so that it continuously recognizes the world's ever-changing bacteria, viruses, fungi, cancer cells and other organisms that attack the human body.

While these modifications are essential to continued health, improper modifications can leave the immune system attacking its own body.

The immune system's first levels of defense are the physical barriers of the innate immune system. These include the skin, tears, and respiratory and digestive tract secretions. Should a foreign organism penetrate one of these barriers and enter the body, the innate immune system begins fighting it off by triggering inflammation and encouraging natural killer cells and macrophages to isolate the foreign antigen and kill it, a process known as phagocytosis.

The responses of the innate immune system are the same for any infectious process and are independent of any antigen. The adaptive immune response is antigen-dependent and designed to eliminate specific antigens; it develops throughout life as an individual is exposed to organisms. Antigens can be a whole cell or organism (e.g., bacteria) or may be a protein, nucleoprotein, lipid or polysaccharide within the foreign material. Once an antigen is recognized, the adaptive immune system can respond in one of two ways: humoral or cellular. Epitopes are the features of antigens that determine which immune response pathway is followed.

Both the humoral and cellular pathways rely on lymphocytes, which are the major cells of the immune system. Lymphocytes are classified as either T- or B-cells, both of which can only identify antigens. The immune system also has natural killer (NK) cells, which attack foreign organisms and abnormal cells without prior stimulation. Lymphocytes and NK cells originate in the bone marrow. B-lymphocytes and NK cells are mature when they leave the bone marrow.

**OBJECTIVES**

- Review the physiology of the immune system
- Describe three examples of how the immune system can become suppressed: HIV, organ transplant immunosuppression and autoimmune disease systemic lupus erythematosus (SLE)
- Discuss patient management and infection control procedures
immune systems are highly susceptible to attack from foreign organisms. Patients otherwise outside of the scope of this article. responsible for most allergic reactions but is IgA, IgM, IgE and IgD. IgE is the antibody determined by the antigen’s epitope. There globulins bind to specific antigens as by B-lymphocytes and plasma cells, immu-

the humoral immune response. Produced Antibodies, also known as immunoglobu-

antigen and alert B-lymphocytes to release these responses, macrophages ingest the these responses, the body’s actual infected tion, most patients have a T-lymphocyte count of less than 700 cells/μL. A count of less than 200 CD4 T-lymphocytes/μL is considered diagnostic for AIDS, the third phase of the disease. For patients with the disease, AIDS is not what ultimately kills them; rather, their lack of ability to fight infections puts them at risk for acquiring an opportunistic infection they’re unable to fight as a result of the lack of T-lymphocytes.

With proper treatment, patients may not develop AIDS for years. Although some patients continue to experience T-lymphocyte count decline, some never develop AIDS and may even see their counts normalize. Expect these patients to be on both antiretroviral drugs and prophylaxis for opportunistic infections. One common side effect of antiretroviral drugs is diarrhea. Crofelemer has been approved for management of this diarrhea provided the patient does not have a GI infection. Remember, continuous diarrhea can lead to dehydration.

A physical on a patient with HIV will reveal no specific findings characteristic of the disease. Rather, it is essential to look for signs of infection. During acute seroconversion the patient may complain of flu-like symptoms and have a fever, malaise and generalized rash. Once seroconversion is complete, the physical findings of an opportunistic infection are the only external signs a patient may be infected.2

Organ Transplants

According to the Organ Procurement and Transplantation Network, more than 44,000 organ transplants occurred in the U.S. since January 2012.3 In the United States, the kidney is the most commonly transplanted organ, followed by the liver, heart and lungs.4

Following organ transplant, the recipient is placed on immunosuppression drugs to decrease the chances of transplant rejection. With aggressive management, one-year graft (the transplanted organ) survival is over 90%. However, this high success rate comes with an increased risk for infection.4 Unfortunately, without this aggressive management, graft success is nearly impossible.

Organ transplant success began with the release of two drugs, Purinethol and azathioprine, in the early 1960s; prior to that all patients had experienced organ
rejection. After these drugs it wasn’t until the 1980s that survival increased as cyclo-sporines, which inhibit the function and production of T-cells, were introduced and replaced Purinethol in the two-drug combo. Then in 1994 mycophenolate mofetil was introduced and replaced azathioprine as a primary immunosuppressant. Mycophenolate (MCA) slows B- and T-cell proliferation by slowing their cell division through enzyme inhibition.

Without immediate immunosuppression and long-term management, the patient’s body will eventually reject and attack a foreign organ like any other antigen. While physicians make every effort to match organ donors and recipients as best they can, only identical twins will have identical tissue antigens. Thus most organ recipients receive organs that have different proteins (antigens). Should the recipient’s body recognize these antigens as foreign, the immune system will attack.

Immediately following an organ recipient’s surgery, immunosuppression begins. The initial immunosuppression phase typically lasts around three months, after which patient enters into their long-term immunosuppression maintenance phase. This is accomplished with the same drugs used for initial suppression, but the doses and patient’s serum levels (concentration in the blood serum) are reduced.

For the rest of a transplant recipient’s life, their immune system must remain suppressed, and they are also at risk for acute organ rejection. Inadequate immunosuppression can cause acute rejection. However, if the patient’s immunosuppressive drugs are already in their therapeutic range, increasing their doses is unlikely to help during acute rejection. Instead, corticosteroids are the primary intervention for acute rejection, as they prevent the release of macrophages and block the synthesis of helper T-cells. The net effect is a near depletion of the immune system, yet reversal of rejection in 75% of cases.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (lupus) is a multifaceted autoimmune disease that affects all organ systems. It is considered a chronic condition that has acute symptomatic flare-ups and is followed by a relapse-type period.

The specific cause of lupus is not known, but research shows a combination of immune system dysfunctions leads to the generation of autoantibodies and microvascular inflammation. Autoantibodies, antibodies that attack the body, are suspected to develop as a result of a defect in apoptosis that results in increased cell death and immune intolerance; however, this is unproven. During a lupus activation, immune antibody-antigen complexes form in the microvasculature, triggering adaptive system activation and inflammation. These complexes also become deposited along the base of the skin and kidney membranes. As tissue damage becomes more widespread, lupus can cause antibody-mediated cytotoxicity, which results in thrombocytopenia, hemolysis and organ dysfunction.

There are about 250,000 individuals with lupus in the United States. Cases may be benign for years or progress rapidly and become fatal. Cases tend to be less serious when the primary organs affected are the skin and muscle groups; it has more serious symptoms when the renal and central nervous systems are affected. Currently 10-year survival exceeds 90%.

The presentation of lupus varies widely, as all organ systems can be affected at different times. A new diagnosis will not be made by prehospital providers. Patients with a history of lupus experiencing flare-ups may complain of fatigue, mild fever, weight changes or joint discomfort. Of these, fatigue is the most common. Patients may also experience mood swings, migraines and difficulty focusing. Some may also say they notice rashes that develop when their skin is exposed to sunlight for an extended period. Patients may complain of chest pain or shortness of breath when inflammation occurs in the pulmonary system. Nausea and vomiting are common complaints during a flare-up but do not specifically indicate gastrointestinal inflammation. Physical exams are nonspecific, as complaints are often vague.

One specific physical finding of lupus is a facial rash. Inspect the face for a malar rash, an erythematous rash spreading across both cheeks and the nose. On occasion the malar rash can be slightly painful. When patients complain of rashes following sun exposure, inspect the skin for discoid lesions, which are often plaquelike lesions in the follicles. Long term, the lesions can cause scarring. On occasion oral ulcers can be noted. Nonspecific findings on the skin can include a broken mottled and erythematous pattern, Raynaud’s phenomenon, bullous lesions, purpura and urticaria. Raynaud’s phenomenon is the spontaneous excessively reduced circulation in the periphery (typically fingers or toes) during sudden exposure to cold or stress. Additionally, joints become swollen when lupus affects them; the most frequently affected are the hands and wrists, as well as the knees. Pain within the joints often seems disproportionate to the swelling.

Infections in patients with lupus are not uncommon. Patients often complain of chest pain; evaluate this carefully, as pericarditis is common and often presents with relief when the patient leans forward. Listening to heart tones may reveal a friction rub or murmur. Rales are often heard when auscultating lung sounds; this suggests pneumonia, particularly when the rales or decreased lung sounds are one-sided.

Patients with lupus are medicated based on the severity of their symptoms and the organ systems affected. If only the integumentary and skeletal systems are involved, the patient may be managed with nonsteroidal anti-inflammatory drugs (NSAIDs) and low-potency immunosuppression drugs. With the more central organ systems, such as the renal, digestive, respiratory and circulatory systems, patients are likely to be on corticosteroids and immunosuppressive drugs such as azathioprine and mycophenolate mofetil.

Patient Management

These patients are likely to chronically be on drugs that minimize their infectious symptoms. Their drugs have the potential for toxicity, and multiple infections are common. Overall, these considerations create difficulty distinguishing underlying illness-related symptoms from new opportunistic infections.

These patients regularly complain of the side effects of immunosuppressive agents. Common side effects include loss of appetite, nausea and vomiting, trembling...
in the hands and feet, weakness and chills. Do not automatically assume patients with these symptoms are having side effects; be a detective and use an organ system-based approach to look for evidence of infection.

Evaluation of a potential solid organ transplant rejection requires laboratory data specific to that organ as well as ruling out other infections. Because rejection suppression is a true specialty of medicine, this management is best performed at the hospital where the transplant occurred. Anticipate that patients with solid organ transplants will want to be taken to the operating hospital; when this isn’t feasible (e.g., due to distance or illness severity) the patient will likely be transported interfacility as soon as an emergency department physician screens and stabilizes them. Patients who have had a kidney transplant are at increased risk for urinary tract infections, lung recipients are at risk for pneumonias, and heart recipients are at risk for pneumonias, pericarditis and the rapid onset of sepsis.

Immunosuppression agents break down most of the major inherent barriers of a healthy immune system. Because of this patients constantly risk exposure to opportunistic infections. Use a thorough history and assessment to try to identify potential infection sources and affected organs. These infections generally follow one of these pathways:4

- Community-acquired infections such as colds, respiratory system infections, MRSA and pneumonias;
- Reactivation of a dormant infection, including from the donor of a transplanted organ; these infections can include herpes, parasites, hepatitis and tuberculosis;
- Epidemiologic exposure based on a patient’s habits, including travel, sexuality, workplace and animal exposure;
- Healthcare-initiated infections, especially a risk when the patient is seen by medical providers who see multiple patients in a given day;
- Travel-associated infections, especially when travel includes foreign countries.

Fever is an ominous symptom of illness in the immunocompromised patient, and at times it may be the only obvious symptom. Assume that any fever is associated with a high-risk infection and ensure safe transport to an emergency department. Even low-grade fevers are considered serious, as many of these patients are on corticosteroids, which can suppress fevers; these are not patients who should be referred to a primary care physician or urgent care.

As you look for evidence of infection within organ systems, be astute for exposures that prehospital providers can control or make worse. For example, an open wound should be cleaned with soap and water prior to transport and dirty pants may require removal, especially if a urinary or gastrointestinal infection is suspected.

Children require special consideration, especially when they are immunocompromised following a solid organ transplant. There are more than 2,000 children in the U.S. with transplanted organs, with the kidney, liver and heart the most common. As part of normal development, the immune system matures as we age. Young children have immature immune systems with greater risk for infection, and when they require organ transplants the immunosuppressive agents greatly increase their risk of infection.

Prevention is paramount when managing immunocompromised patients, as their infections are more easily prevented than eliminated. One of the most effective and important strategies for infection prevention is use of proper hand hygiene. In general, roughly 1 of 20 patients acquire an infection while hospitalized.7 Wearing gloves is not enough to prevent the spread of an infection from one patient to another. Proper hand washing—scrubbing all surfaces for 40–60 seconds—is the standard. Use enough soap to cover all of the hands’ surfaces before scrubbing and rinsing. When arriving on the scene of an ill immunocompromised patient, it is worth taking the time to ask permission and wash your hands prior to donning gloves to evaluate the patient.

Additionally, it may be beneficial when interacting with an immunocompromised patient to take a few minutes to ensure there is low risk for exposure inside the ambulance. While an ambulance should always be cleaned in between transports, it simply doesn’t always happen. If you are in doubt about the ambulance’s or stretcher’s cleanliness (not just dirt but microbes too), take a few moments to wipe down the surfaces with a 10% bleach solution or other approved cleanser. Transporting these patients in an ambulance with latent viruses or bacteria may unnecessarily expose them to infection.

During transport, patient interventions are symptom-based. Oxygen may be applied via nasal cannula to maintain an SpO₂ around 94%. It is appropriate to initiate intravenous access and, if allowed, draw blood cultures and labs. Administration of IV fluids is typically unnecessary unless the patient has evidence of sepsis.

Remember, fevers are a symptom of infection, and in the immunocompromised patient may be your only symptom. Fevers can be symptomatically treated with 5 mg/kg of acetaminophen (1 gram maximum dose) as long as protocols permit it and the patient can swallow. Acetaminophen will reduce the fever and increase patient comfort, and will not impair a physician’s assessment.

Neutropenic fevers develop when a patient with neutropenia (critically low neutrophil levels) develops an infection. Neutrophils are a type of white blood cell that kills bacteria and make up 50%–70% of the white blood cell count. Patients with suppressed immune systems are at risk for neutropenia. When patients with low white blood cell counts are found to be febrile, the fever is considered a neutropenic fever. This is a medical emergency, as the patient lacks the ability to fight off the developing infection.

Medical providers must wear masks, gloves and gowns at all times. EMS providers should never allow these patients to be transported with other patients or extra passengers. Further, these patients must be managed with extra oral and intravenous fluids compared to healthy individuals. Don’t be surprised to find patients with neutropenia at home; their environment must be kept particularly clean and free of any plants or other materials that are bacteria-prone, their food thoroughly cooked, and clothing and sheets kept impeccably clean.
Introduction — Sepsis is a clinical syndrome that has physiologic, biologic, and biochemical abnormalities caused by a dysregulated inflammatory response to infection. Sepsis and the inflammatory response that ensues can lead to multiple organ dysfunction syndrome and death.

The epidemiology, definitions, risk factors, clinical presentation, diagnosis, and outcomes of sepsis are reviewed here. The pathophysiology and treatment of sepsis are discussed separately. (See "Pathophysiology of sepsis" and "Evaluation and management of suspected sepsis and septic shock in adults").

Epidemiology

Incidence — In the late 1970s, it was estimated that 164,000 cases of sepsis occurred in the United States (US) each year [1]. Since then, rates of sepsis in the US and elsewhere have on balance increased although many of these are derived from academic institutions or on claims-based analyses [2-5]:

- One national database analysis of discharge records from hospitals in the US estimated an annual rate of more than 1,665,000 cases of sepsis between 1979 and 2000 [2].

- Another retrospective population-based analysis reported increased rates of sepsis and septic shock from 13 to 78 cases per 100,000 between 1998 and 2009 [3].

- A retrospective analysis of an international database reported a global incidence of 437 per 100,000 person-years for sepsis between the years 1995 and 2015, although this rate was not reflective of contributions from low- and middle-income countries [6].

- In an analysis of 27 academic hospitals, between 2005 and 2014 rates of septic shock determined by clinical criteria increased from 12.8 to 18.6 per 1000 hospital admissions and mortality decreased from 55 to 51 percent [7]. Similar trends were noted when the International Classification of Diseases 9th edition (ICD 9) codes were used except the decrease in mortality was more dramatic.

- In contrast, a 2017 study reports stable rates of sepsis between 2009 and 2014 [8]. This study used clinical electronic health record (EHR) data (and the sepsis definitions described above (see 'Sepsis' below)) from 7 million hospitalizations in 409 US hospitals and compared it to traditional claims-based analysis (International Classification of diseases, Ninth Revision, Clinical Modification codes for severe sepsis or septic shock) and direct chart review. It was estimated that using EHR-based data, admission rates due to sepsis remained unchanged over the study period at 6 percent while in-hospital mortality decreased by 3
percent. In contrast, claims-based analyses suggested a 10 percent increase in incidence and a 7 percent reduction in mortality. When compared with direct chart review (thought to be the most sensitive method of detecting incidence) of 510 randomly selected cases, it was estimated that EHR-based analyses missed 20 percent of sepsis cases, while claims-based analysis missed 40 percent.

Reasons for a possible increased rate of sepsis include advancing age, immunosuppression, and multidrug-resistant infection [4,9-12]. It may also be due to the increased detection of early sepsis from aggressive sepsis education and awareness campaigns, although this hypothesis is unproven.

The incidence of sepsis varies among the different racial and ethnic groups, but appears to be highest among African-American males (figure 1) [1].

The incidence is also greatest during the winter, probably due to the increased prevalence of respiratory infections [13].

Older patients ≥65 years of age account for the majority (60 to 85 percent) of all episodes of sepsis; with an increasing aging population, it is likely that the incidence of sepsis will continue to increase in the future [1,4,14,15].

**Pathogens** — The contribution of various infectious organisms to the burden of sepsis has changed over time [16-18]. Gram positive bacteria are most frequently identified in patients with sepsis in the United States, although the number of cases of Gram negative sepsis remains substantial. The incidence of fungal sepsis has increased over the past decade, but remains lower than bacterial sepsis [1]. In approximately half of cases of sepsis, an organism is not identified (culture negative sepsis) [19].

**Disease severity** — The severity of disease appears to be increasing [20]. In one retrospective analysis, the proportion of patients with sepsis who also had at least one dysfunctional organ increased from 26 to 44 percent between 1993 and 2003 [21,22]. The most common manifestations of severe organ dysfunction were acute respiratory distress syndrome, acute renal failure, and disseminated intravascular coagulation [23]. However, it is unclear as to whether the rising incidence of sepsis and septic shock reflects the overall increased incidence of sepsis or altered definitions of sepsis over time.

**DEFINITIONS** — Sepsis exists on a continuum of severity ranging from infection and bacteremia to sepsis and septic shock, which can lead to multiple organ dysfunction syndrome (MODS) and death. The definitions of sepsis and septic shock have rapidly evolved since the early 1990s [24-29]. The systemic inflammatory response syndrome (SIRS) is no longer included in the definition since it is not always caused by infection. The definitions for sepsis that we provide below reflect expert opinion from task forces generated by national societies including the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM). Importantly, such definitions are not diagnostic of sepsis since they do not comprehensively include specific criteria for the identification of infection. However, clinicians should be aware that SCCM/ESICM definitions are not unanimously accepted. For example, the Center for Medicare and Medicaid Services (CMS) still continues to support the previous definition of SIRS, sepsis, and severe sepsis. (See ‘Diagnosis’ below.)

**Early sepsis** — Infection and bacteremia may be early forms of infection that can progress to sepsis. However, there is no formal definition of early sepsis. Nonetheless, despite the lack of definition, monitoring those suspected of having sepsis is critical for its prevention.

**Infection and bacteremia** — All patients with infection or bacteremia are at risk of developing sepsis and represent early phases in the continuum of sepsis severity:

- Infection is defined as the invasion of normally sterile tissue by organisms resulting in infectious pathology.
- Bacteremia is the presence of viable bacteria in the blood.

**Identification of early sepsis (qSOFA)** — Societal guidelines place emphasis on the early identification of infected patients who may go on to develop sepsis as a way to decrease sepsis-associated mortality. The 2016 SCCM/ESICM task force have described an assessment score for patients outside the intensive care unit as a way to facilitate the identification of patients potentially at risk of dying from sepsis [27-29]. This score is a modified version of the Sequential (Sepsis-related) Organ Failure Assessment score (SOFA) called the quickSOFA (qSOFA) score. A score ≥2 is associated with poor outcomes due to sepsis.

The qSOFA score is easy to calculate since it only has three components, each of which are readily identifiable at the bedside and are allocated one point:

- Respiratory rate ≥22/minute
- Altered mentation
- Systolic blood pressure ≤100 mmHg

The qSOFA score was originally validated in 2016 as most useful in patients suspected as having sepsis outside of the intensive care unit (ICU) [29]. It has since been prospectively validated in the emergency department (ED) and confirmed to be less valuable in the ICU setting [30,31]. Among 879 patients presenting to the ED with suspected infection, the predictive validity of qSOFA for in hospital mortality was similar to that of the full SOFA score (3 percent mortality for qSOFA and SOFA scores less than 2 versus 24 and 18 percent mortality for qSOFA and SOFA scores greater than or equal to 2, respectively). In addition, qSOFA was superior to the systemic inflammatory response syndrome criteria (SIRS) (area under the receiver operating curve [AUROC], 0.80 versus 0.65) [30]. In contrast, a retrospective analysis of 184,875 ICU patients with an infection-related diagnosis reported that qSOFA was inferior to SOFA in predicting in hospital mortality (AUROC, 0.75 versus 0.60) [31]. Limitations of these analyses include a high percentage of missing values [30] and poor generalizability to all EDs or ICUs as well as to lower- and middle-income settings [30,31]. Despite these encouraging results, we believe that further studies that demonstrate improved clinically meaningful outcomes due to the use of qSOFA compared to clinical judgement are warranted before it can be routinely used to predict in hospital mortality. In support, one study reported that other early identification scores including the modified early warning score (MEWS), the national early warning score (NEWS), and SIRS outperformed qSOFA for predicting death and ICU transfer in non-ICU patients [32].

The full SOFA score is described separately. (See "Predictive scoring systems in the intensive care unit", section on 'Sequential (sepsis-related) Organ Failure Assessment (SOFA)' and 'Sepsis' below.)

**Sepsis** — A 2016 SCCM/ESICM task force has defined sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection:

- **Organ dysfunction** — Organ dysfunction is defined by the 2016 SCCM/ESICM task force as an increase of two or more points in the SOFA score (calculator 1). The validity of this score was derived from critically-ill patients with suspected sepsis by interrogating over a million intensive care unit (ICU) electronic health record encounters from ICUs both inside and outside the United States [27-29]. ICU patients were suspected as having infection if body fluids were cultured and they received antibiotics. Predictive scores (SOFA, systemic inflammatory response syndrome [SIRS], and logistic Organ Dysfunction System [LODS]) were compared for their ability to predict mortality. Among critically ill patients with suspected sepsis, the predictive validity of the SOFA score for in-hospital mortality was superior to that for the SIRS criteria (area under the receiver operating characteristic curve 0.74 versus 0.64). Patients who fulfill these criteria have a predicted mortality of ≥10 percent. Although the predictive capacity of SOFA and LODS were similar, SOFA is considered easier to calculate, and was therefore recommended by the task force.
Importantly, the SOFA score is an organ dysfunction score. It is not diagnostic of sepsis nor does it identify those whose organ dysfunction is truly due to infection but rather helps identify patients who potentially have a high risk of dying from infection. In addition, it does not determine individual treatment strategies nor does it predict mortality based upon demographics (eg, age) or underlying condition (eg, stem cell transplant recipient versus postoperative patient). SOFA and other predictive scores are discussed separately. (See "Predictive scoring systems in the intensive care unit", section on 'Sequential (sepsis-related) Organ Failure Assessment (SOFA').)

- **Infection** – There are no clear guidelines to help the clinician identify the presence of infection or to causally link an identified organism with sepsis. In our experience, for this component of the diagnosis, the clinician is reliant upon clinical suspicion derived from the signs and symptoms of infection as well as supporting radiologic and microbiologic data and response to therapy. (See 'Clinical presentation' below and 'Diagnosis' below.)

The term severe sepsis, which originally referred to sepsis that was associated with tissue hypoperfusion (eg, elevated lactate, oliguria) or organ dysfunction (eg, elevated creatinine, coagulopathy) [25,33], and the term systemic inflammatory response syndrome (SIRS [table 1]) are no longer used since the 2016 sepsis and septic shock definitions include patients with evidence of tissue hypoperfusion and organ dysfunction. However, the Center for Medicare and Medicaid Services (CMS) still continues to support the previous definition of SIRS, sepsis, and severe sepsis.

**Septic shock** — Septic shock is a type of vasodilatory or distributive shock. Septic shock is defined as sepsis that has circulatory, cellular, and metabolic abnormalities that are associated with a greater risk of mortality than sepsis alone [27]. Clinically, this includes patients who fulfill the criteria for sepsis (see 'Sepsis' above) who, despite adequate fluid resuscitation, require vaspressors to maintain a mean arterial pressure (MAP) ≥65 mmHg and have a lactate >2 mmol/L (>18 mg/dL). Per predictions from the SOFA score (calculator 1), patients who fulfill these criteria for septic shock have a higher mortality than those who do not (≥40 versus ≥10 percent). (See "Predictive scoring systems in the intensive care unit", section on 'Sequential (sepsis-related) Organ Failure Assessment (SOFA').)

**Others** — Multiple organ dysfunction syndrome (MODS) and systemic inflammatory response syndrome (SIRS) are terms frequently used in practice that need to be distinguished from sepsis.

**Multiple organ dysfunction syndrome** — Multiple organ dysfunction syndrome (MODS) refers to progressive organ dysfunction in an acutely ill patient, such that homeostasis cannot be maintained without intervention. It is at the severe end of the severity of illness spectrum of both infectious (sepsis, septic shock) and noninfectious conditions (eg, SIRS from pancreatitis). MODS can be classified as primary or secondary:

- Primary MODS is the result of a well-defined insult in which organ dysfunction occurs early and can be directly attributable to the insult itself (eg, renal failure due to rhabdomyolysis).

- Secondary MODS is organ failure that is not in direct response to the insult itself, but is a consequence of the host's response (eg, acute respiratory distress syndrome in patients with pancreatitis).

There are no universally accepted criteria for individual organ dysfunction in MODS. However, progressive abnormalities of the following organ-specific parameters are commonly used to diagnose MODS and are also used in scoring systems (eg, SOFA (calculator 1) or LODS) to predict ICU mortality [34-36] (see "Predictive scoring systems in the intensive care unit"):

- Respiratory – Partial pressure of arterial oxygen (PaO₂)/fraction of inspired oxygen (FiO₂) ratio
- Hematology – Platelet count
- Liver – Serum bilirubin
• Renal – Serum creatinine (or urine output)
• Brain – Glasgow coma score
• Cardiovascular – Hypotension and vasopressor requirement

In general, the greater the number of organ failures, the higher the mortality, with the greatest risk being associated with respiratory failure requiring mechanical ventilation. (See "Acute respiratory distress syndrome: Prognosis and outcomes in adults").

**Systemic inflammatory response syndrome** — The use of systemic inflammatory response syndrome (SIRS) criteria to identify those with sepsis has fallen out of favor since it is considered by many experts that SIRS criteria are present in many hospitalized patients who do not develop infection, and their ability to predict death is poor when compared with other scores such as the SOFA score [29,37,38]. SIRS is considered a clinical syndrome that is a form of dysregulated inflammation. It was previously defined as two or more abnormalities in temperature, heart rate, respiration, or white blood cell count [25]. SIRS may occur in several conditions related, or not, to infection. Noninfectious conditions classically associated with SIRS include autoimmune disorders, pancreatitis, vasculitis, thromboembolism, burns, or surgery.

**Pregnancy** — The usual scoring systems (eg, SOFA, SIRS) have excluded pregnant women because pregnancy physiology is different and normal pregnancy parameters overlap with criteria for sepsis [39] such that some experts have proposed use of pregnancy-specific scores. As an example, the sepsis in obstetrics score is a score that incorporates clinical criteria, modified for parameters expected to change in pregnancy, that predicted risk of admission to the intensive care unit with a score of six or greater [40]. Further validation of this score is needed before it can be routinely used in this population. Guidelines have been proposed by some experts for potential diagnostic parameters but have not been universally accepted or validated [41].

**RISK FACTORS** — The importance of identifying risk factors for sepsis was highlighted in one epidemiologic study that reported that risk factors for septic shock were the fifth leading cause of years of productive life lost due to premature mortality [42]. Risk factors for sepsis include the following [43-52]:

• **Intensive care unit admission** – Approximately 50 percent of intensive care unit (ICU) patients have a nosocomial infection and are, therefore, intrinsically at high risk for sepsis [53].

• **Bacteremia** – Patients with bacteremia often develop systemic consequences of infection. In a study of 270 blood cultures, 95 percent of positive blood cultures were associated with sepsis, or septic shock [48].

• **Advanced age (≥65 years)** – The incidence of sepsis is disproportionately increased in older adult patients and age is an independent predictor of mortality due to sepsis. Moreover, older adult non-survivors tend to die earlier during hospitalization and older adult survivors more frequently require skilled nursing or rehabilitation after hospitalization [49].

• **Immunosuppression** – Comorbidities that depress host-defense (eg, neoplasms, renal failure, hepatic failure, AIDS, asplenism) and immunosuppressant medications are common among patients with sepsis, or septic shock. (See "Clinical features and management of sepsis in the asplenic patient").

• **Diabetes and cancer** – Diabetes and some cancers may alter the immune system, result in an elevated risk for developing sepsis, and increase the risk of nosocomial sepsis.

• **Community acquired pneumonia** – Severe sepsis (as defined by the old definition) and septic shock develop in approximately 48 and 5 percent, respectively, of patients hospitalized with community-acquired pneumonia [50].

• **Previous hospitalization** – Hospitalization is thought to induce an altered human microbiome, particularly in patients who are treated with antibiotics. Previous hospitalization has been associated with a three-fold increased risk of developing sepsis in the subsequent 90 days [51]. Patients with hospitalizations for infection-related conditions, especially *Clostridium difficile* infection, are at greatest risk.

• **Genetic factors** – Both experimental and clinical studies have confirmed that genetic factors can increase the risk of infection. In few cases, monogenic defects underlie vulnerability to specific infection, but genetic factors are typically genetic polymorphisms. Genetic studies of susceptibility to infection have initially focused on defects of antibody production, or a lack of T cells, phagocytes, natural killer cells, or complement. Recently, genetic defects have been identified that impair recognition of pathogens by the innate immune system, increasing susceptibility to specific classes of microorganisms [52].

**CLINICAL PRESENTATION** — Patients with suspected or documented sepsis typically present with hypotension, tachycardia, fever, and leukocytosis. As severity worsens, signs of shock (eg, cool skin and cyanosis) and organ dysfunction develop (eg, oliguria, acute kidney injury, altered mental status) [25,33]. Importantly, the presentation is nonspecific such that many other conditions (eg, pancreatitis, acute respiratory distress syndrome) may present similarly. Detailed discussion of the clinical features of shock are discussed separately. (See "Evaluation of and initial approach to the adult patient with undifferentiated hypotension and shock", section on 'Clinical manifestations'.)

**Symptoms and signs** — The symptoms and signs of sepsis are nonspecific but may include the following:

• Symptoms and signs specific to an infectious source (eg, cough dyspnea may suggest pneumonia, pain and purulent exudate in a surgical wound may suggest an underlying abscess).

• Arterial hypotension (eg, systolic blood pressure [SBP] <90 mmHg, mean arterial pressure [MAP] <70 mmHg, an SBP decrease >40 mmHg, or less than two standard deviations below normal for age). Because a sphygmomanometer may be unreliable in hypotensive patients, an arterial catheter may be needed. (See "Arterial catheterization techniques for invasive monitoring").

• Temperature >38.3 or <36°C.

• Heart rate >90 beats/min or more than two standard deviations above the normal value for age.

• Tachypnea, respiratory rate >20 breaths/minute.

• Signs of end-organ perfusion:
  - Warm, flushed skin may be present in the early phases of sepsis. As sepsis progresses to shock, the skin may become cool due to redirection of blood flow to core organs. Decreased capillary refill, cyanosis, or mottling may indicate shock.
  - Additional signs of hypoperfusion include altered mental status, obtundation or restlessness, and oliguria or anuria.
  - Ileus or absent bowel sounds are often an end-stage sign of hypoperfusion.

These findings may be modified by preexisting disease or medications. As examples, older patients, diabetic patients, and patients who take beta-blockers may not exhibit an appropriate tachycardia as blood pressure falls. In contrast, younger patients frequently develop a severe and prolonged tachycardia and fail to become hypotensive until acute decompensation later occurs, often suddenly. Patients with chronic hypertension may develop critical hypoperfusion at a higher blood pressure than healthy patients (ie, relative hypotension).
**Laboratory signs** — Similarly, laboratory features are nonspecific and may be associated with abnormalities due to the underlying cause of sepsis or to tissue hypoperfusion or organ dysfunction from sepsis. They include the following:

- Leukocytosis (white blood cell [WBC] count >12,000 microL^{-1}) or leukopenia (WBC count <4000 microL^{-1}) (table 2).
- Normal WBC count with greater than 10 percent immature forms.
- Hyperglycemia (plasma glucose >140 mg/dL or 7.7 mmol/L) in the absence of diabetes.
- Plasma C-reactive protein more than two standard deviations above the normal value.
- Arterial hypoxemia (arterial oxygen tension [PaO2]/fraction of inspired oxygen [FiO2] <300).
- Acute oliguria (urine output <0.5 mL/kg/hour for at least two hours despite adequate fluid resuscitation).
- Creatinine increase >0.5 mg/dL or 44.2 micromol/L.
- Coagulation abnormalities (international normalized ratio [INR] >1.5 or activated partial thromboplastin time [aPTT] >60 seconds).
- Thrombocytopenia (platelet count <100,000 microL^{-1}).
- Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 micromol/L).
- Adrenal insufficiency (eg, hyponatremia, hyperkalemia), and the euthyroid sick syndrome can also be found in sepsis.
- Hyperlactatemia (higher than the laboratory upper limit of normal) – An elevated serum lactate (eg, >2 mmol/L) can be a manifestation of organ hypoperfusion in the presence or absence of hypotension and is an important component of the initial evaluation, since elevated lactate is associated with poor prognosis [33,54-56]. A serum lactate level ≥4 mmol/L is consistent with, but not diagnostic of, septic shock. Additional laboratory studies that help characterize the severity of sepsis include a low platelet count, and elevated international normalized ratio, creatinine, and bilirubin.
- Plasma procalcitonin more than two standard deviations above the normal value (not routinely performed in many centers) – Elevated serum procalcitonin levels are associated with bacterial infection and sepsis [57-59]. Despite this, a meta-analysis of 18 studies found that procalcitonin did not readily distinguish sepsis from nonseptic systemic inflammation (sensitivity of 71 percent and specificity of 71 percent) [58]. (See "Evaluation and management of suspected sepsis and septic shock in adults", section on 'De-escalation and duration of antibiotics'.)

**Imaging** — There are no radiologic signs that are specific to the identification of sepsis other than those associated with infection in a specific site (eg, pneumonia on chest radiography, fluid collection on computed tomography of the abdomen).

**Microbiology** — The identification of an organism in culture in a patient who fulfills the definition of sepsis (see 'Sepsis' above) is highly supportive of the diagnosis of sepsis but is not necessary. The rationale behind its lack of inclusion in the diagnostic criteria for sepsis is that a culprit organism is frequently not identified in up to 50 percent of patients who present with sepsis nor is a positive culture required to make a decision regarding treatment with empiric antibiotics [19,60].
DIAGNOSIS — A limitation of the definitions above (see "Definitions" above) is that they cannot identify patients whose organ dysfunction is truly secondary to an underlying infection. Thus, a constellation of clinical, laboratory, radiologic, physiologic, and microbiologic data is typically required for the diagnosis of sepsis and septic shock. The diagnosis is often made empirically at the bedside upon presentation, or retrospectively when followup data returns (eg, positive blood cultures in a patient with endocarditis) or a response to antibiotics is evident. Importantly, the identification of a culprit organism, although preferred, is not always feasible since in many patients no organism is ever identified. In some patients this may be because they have been partially treated with antibiotics before cultures are obtained.

Although septic shock has a specific hemodynamic profile on pulmonary artery catheterization (PAC) (table 3), PACs are difficult to interpret and rarely placed in patients with suspected sepsis. (See "Pulmonary artery catheterization: Interpretation of hemodynamic values and waveforms in adults" and "Evaluation of and initial approach to the adult patient with undifferentiated hypotension and shock", section on 'Pulmonary artery catheterization'.)

The evaluation and diagnosis of shock is discussed separately. (See "Evaluation of and initial approach to the adult patient with undifferentiated hypotension and shock".)

PROGNOSIS

In-hospital morbidity and mortality — Sepsis has a high mortality rate. Rates depend upon how the data are collected but estimates range from 10 to 52 percent [1,4,21,37,61-70]. Data derived from death certificates report that sepsis is responsible for 6 percent of all deaths while administrative claims data suggest higher rates [70]. Mortality rates increase linearly according to the disease severity of sepsis [37]. In one study, the mortality rates of SIRS, sepsis, and septic shock were 7, 16, and 46 percent, respectively [23]. In another study, the mortality associated with sepsis was ≥10 percent while that associated with septic shock was ≥40 percent [27]. Mortality appears to be lower in younger patients (<44 years) without comorbidities (<10 percent) [4].

Several studies have reported decreasing mortality rates over time [1,4,21,65,71,72]. As an example, a 12-year study of 101,064 patients with sepsis and septic shock from 171 intensive care units (ICUs) in Australia and New Zealand reported a 50 percent risk reduction (from 35 to 18 percent) in in-hospital mortality from 2000 to 2012 [4]. This persisted after adjusting for multiple variables including underlying disease severity, comorbidities, age, and the rise in incidence of sepsis over time. This suggested that the reduction in mortality observed in this study was less likely due to the increased detection of early sepsis and possibly due to improved therapeutic strategies for sepsis. However, despite improved compliance with practice guidelines for the treatment of sepsis (also known as sepsis bundles), compliance rates vary and there is conflicting evidence as to whether sepsis bundles truly improve mortality [3,65,67,73-77].

During hospital admission, sepsis may increase the risk of acquiring a subsequent hospital-related infection. One prospective observational study of 3329 admissions to the ICU reported that ICU-acquired infections occurred in 13.5 percent admissions of patients with sepsis compared with 15 percent of non-sepsis ICU admissions [78]. Patients admitted with sepsis also developed more ICU-acquired infections including infection with opportunistic pathogens, hinting at possible immune suppression. In patients with a sepsis admission diagnosis, secondary infections were mostly catheter-related blood stream infections (26 percent), pneumonia (25 percent), or abdominal infections (16 percent), compared with patients with non-sepsis admission where pneumonia was the most common ICU-acquired infection (48 percent). In both groups, patients who developed ICU-acquired infection were more severely ill on admission (eg, higher Acute Physiologic and Chronic Health Evaluation [APACHE] IV and Sequential Organ Failure Assessment scores and more shock on admission) and had higher mortality at day 60. However, the contribution of developing a secondary infection was small.
**Long-term prognosis** — Following discharge from the hospital, sepsis carries an increased risk of death (up to 20 percent) as well as an increased risk of further sepsis and recurrent hospital admissions (up to 10 percent are readmitted). Most deaths occur within the first six months but the risk remains elevated at two years [79-87]. Patients who survive sepsis are more likely to be admitted to acute care and/or long term care facilities in the first year after the initial hospitalization, and also appear to have a persistent decrement in their quality of life [64,81-83].

The most common diagnoses associated with readmission at 90 days in one database analysis of 3494 hospital admissions included heart failure, pneumonia, acute exacerbations of chronic obstructive pulmonary disease, and urinary tract infections [84]. Higher rates of readmission with subsequent infection and sepsis may be associated with previous hospitalization for an infection, particularly infection with *clostridium difficile* [51,88]. Another database analysis reported that a previous diagnosis of sepsis was a leading cause of readmissions when compared with myocardial infarction, chronic obstructive pulmonary disease, heart failure, and pneumonia [89]. Sepsis survivors may also be at increased risk of major cardiovascular events and stroke when compared with patients hospitalized with nonsepsis diagnosis [87,90]. (See "Hospital discharge and readmission").

**Prognostic factors** — Clinical characteristics that impact the severity of sepsis and, therefore, the outcome include the host's response to infection, the site and type of infection, and the timing and type of antimicrobial therapy.

**Host-related** — Anomalies in the host's inflammatory response may indicate increased susceptibility to severe disease and mortality. As examples, the failure to develop a fever (or hypothermia) and the development of leukopenia, thrombocytopenia, hyperchloremia, a patient's comorbidities, age, hyperglycemia, hypocoagulability, and failure of procalcitonin to fall have all been associated with poor outcomes [91-98].

Failure to develop a fever (defined as a temperature below 35.5°C) was more common among non-survivors of sepsis than survivors (17 versus 5 percent) in one study of 519 patients with sepsis [91]. Leukopenia (a white blood count less than 4000/mm³) was similarly more frequent among non-survivors than survivors (15 versus 7 percent) in a study of 612 patients with Gram negative sepsis [93] and a platelet count <100,000/mm³ was found to be an early prognostic marker of 28-day mortality in another study of 1486 patients with septic shock [96]. In another retrospective analysis of critically ill septic patients, hyperchloremia (Cl ≥110 mEq/L) at 72 hours after ICU admission was independently associated with an increase in all-cause hospital mortality [95].

A patient's comorbidities and functional health status are also important determinants of outcome in sepsis [91]. Risk factors for mortality include new-onset atrial fibrillation [99,100], an age above 40 years [14], and comorbidities such as AIDS [101], liver disease [102], cancer [103], alcohol dependence [102], and/or immune suppression [101,104].

Age is probably a risk factor for mortality because of its association with comorbid illnesses, impaired immunologic responses, malnutrition, increased exposure to potentially resistant pathogens in nursing homes, and increased utilization of medical devices, such as indwelling catheters and central venous lines [1,14,105].

Admission hyperglycemia, was found in one prospective observational study of 987 patients with sepsis to be associated with an increased risk of death (hazard ratio 1.66) that was unrelated to the presence of diabetes [97].

Inability to clot has also been associated with increased mortality. In one prospective study of 260 patients with sepsis, indicators of hypocoagulability using standard and functional levels of fibrinogen, were associated with a six-fold increase in the risk of death, particularly in patients treated with hydroxyethyl starch [94].

Failure of procalcitonin level to fall in one study predicted mortality [98]. When procalcitonin did not decrease by more than 80 percent from baseline to day four in patients with severe sepsis, the 28-day mortality was reported...
to be higher (20 versus 10 percent).

**Site of infection** — The site of infection in patients with sepsis may be an important determinant of outcome, with sepsis from a urinary tract infection generally being associated with the lowest mortality rates [91,106]. One study found that mortality from sepsis was 50 to 55 percent when the source of infection was unknown, gastrointestinal, or pulmonary, compared with only 30 percent when the source of infection was the urinary tract [106]. Another retrospective, multicenter cohort study of nearly 8000 patients with septic shock reported similar results with the highest mortality in those with sepsis from ischemic bowel (78 percent) and the lowest rates in those with obstructive uropathy-associated urinary tract infection (26 percent) [69].

Approximately 50 percent of patients with sepsis are bacteremic at the time of diagnosis according to one study [107]. This is consistent with a study of 85,750 hospital admissions, which found that the incidence of positive blood cultures increased along a continuum, ranging from 17 percent of patients with sepsis to 69 percent with septic shock [108]. However, the presence or absence of a positive blood culture does not appear to influence the outcome, suggesting that prognosis is more closely related to the severity of sepsis than the severity of the underlying infection [108,109].

**Type of infection** — Sepsis due to nosocomial pathogens has a higher mortality than sepsis due to community-acquired pathogens [110,111]. Increased mortality is associated with bloodstream infections due to methicillin-resistant staphylococcus aureus (odds ratio 2.70, 95% CI 2.03-3.58), non-candidal fungus (odds ratio 2.66, 95% CI 1.27-5.58), candida (odds ratio 2.32 95% CI 1.21-4.45), methicillin-sensitive staphylococcus aureus (odds ratio 1.9, 95% CI 1.53-2.36), and pseudomonas (odds ratio 1.6, 95% CI 1.04-2.47), as well as polymicrobial infections (odds ratio 1.69, 95% CI 1.24-2.30) [110,112]. When bloodstream infections become severe (eg, septic shock), the outcome is similar regardless of whether the pathogens are Gram-negative or Gram-positive bacteria [44,113].

**Antimicrobial therapy** — Studies have shown that the early administration of appropriate antibiotic therapy (ie, antibiotics to which the pathogen is sensitive) has a beneficial impact on bacteremic sepsis [93,109]. In one report, early institution of adequate antibiotic therapy was associated with a 50 percent reduction in the mortality rate compared to antibiotic therapy to which the infecting organisms were resistant [93]. In contrast, prior antibiotic therapy (ie, antibiotics within the past 90 days) may be associated with increased mortality, at least among patients with Gram negative sepsis [114]. This is probably because patients who have received prior antibiotic therapy are more likely to have higher rates of antibiotic resistance, making it less likely that appropriate antibiotic therapy will be chosen empirically. Empiric antibiotic regimens for patients with suspected sepsis are discussed separately. (See "Evaluation and management of suspected sepsis and septic shock in adults", section on 'Septic focus identification and source control'.)

**Restoration of perfusion** — Failure to aggressively try to restore perfusion early (ie, failure to initiate early goal-directed therapy) may also be associated with mortality [115]. A severely elevated lactate (>4 mmol/L) is associated with a poor prognosis in patients with sepsis with one study reporting a mortality of 78 percent in a population of critically ill patients, a third of whom had sepsis [56]. Restoration of perfusion is discussed in detail separately. (See "Evaluation and management of suspected sepsis and septic shock in adults", section on 'Initial resuscitative therapy'.)

**SOCIETY GUIDELINE LINKS** — Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Sepsis in children and adults".)

**INFORMATION FOR PATIENTS** — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition.
These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topic (see "Patient education: Sepsis in adults (The Basics)"

**SUMMARY AND RECOMMENDATIONS**

- Sepsis is the consequence of a dysregulated inflammatory response to an infectious insult. Global rates of sepsis are as high as 437 per 100,000 person-years and sepsis appears to be responsible for 6 percent of US hospital admissions. Gram positive bacteria are the pathogens that are most commonly isolated from patients with sepsis. (See 'Introduction' above and 'Epidemiology' above.)

- Sepsis exists on a continuum of severity ranging from infection (invasion of sterile tissue by organisms) and bacteremia (bacteria in the blood) to sepsis and septic shock, which can lead to multiple organ dysfunction syndrome (MODS) and death. A 2016 task force from the Society of Critical Care Medicine and European Society of Intensive Care Medicine (SCCM/ESICM) define sepsis and septic shock as the following (see 'Definitions' above):
  
  - Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection; organ dysfunction is defined as an increase of two or more points in the sequential (sepsis-related) organ failure assessment (SOFA) score (calculator 1).

  - Septic shock is defined as sepsis that has circulatory, cellular, and metabolic abnormalities that are associated with a greater risk of mortality than sepsis alone; these abnormalities can be clinically identified as patients who fulfill the criteria for sepsis who, despite adequate fluid resuscitation, require vasopressors to maintain a mean arterial pressure (MAP) ≥65 mmHg and have a lactate >2 mmol/L (>18 mg/dL).

However, clinicians should be aware that SCCM/ESICM definitions are not unanimously accepted. For example, the Center for Medicare and Medicaid Services (CMS) still continues to support the previous definition of systemic inflammatory response syndrome (SIRS (table 1)), sepsis, and severe sepsis.

- Risk factors for sepsis include intensive care unit (ICU) admission, a nosocomial infection, bacteremia, advanced age, immunosuppression, previous hospitalization (in particular hospitalization associated with infection), and community-acquired pneumonia. Genetic defects have also been identified that may increase susceptibility to specific classes of microorganisms. (See 'Risk factors' above.)

- Patients with suspected or documented sepsis typically present with hypotension, tachycardia, fever, and leukocytosis. As severity worsens, signs of shock (eg, cool skin and cyanosis) and organ dysfunction develop (eg, oliguria, acute kidney injury, altered mental status) [25,33]. Importantly, the presentation is nonspecific such that many other conditions (eg, pancreatitis, acute respiratory distress syndrome) may present similarly. (See 'Clinical presentation' above.)

- A constellation of clinical, laboratory, radiologic, physiologic, and microbiologic data is typically required for the diagnosis of sepsis and septic shock. The diagnosis is often made empirically at the bedside upon presentation, or retrospectively when follow-up data return or a response to antibiotics is evident.
Importantly, the identification of a culprit organism, although preferred, is not always feasible since many patients have been partially treated with antibiotics before cultures are obtained. (See 'Diagnosis' above.)

- Sepsis has a high mortality rate that appears to be decreasing. Estimates range from 10 to 52 percent with rates increasing linearly according to the disease severity of sepsis. Following discharge from the hospital, sepsis carries an increased risk of death as well as an increased risk of further sepsis and recurrent hospital admissions. Poor prognostic factors include the inability to mount a fever, leukopenia, age >40 years, certain comorbidities (e.g., AIDS, hepatic failure, cirrhosis, cancer, alcohol dependence, immunosuppression), a non-urinary source of infection, a nosocomial source of infection, and inappropriate or late antibiotic coverage. (See 'Prognosis' above.)

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REFERENCES


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