

Sepsis

3.5 contact hours: \$24

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Course Summary: A clear look at the growing problem of sepsis, including its epidemiology, pathophysiology, diagnosis, management, and prognosis. The course addresses proactive efforts to stem the tide of sepsis in our healthcare system.

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Course Objectives

When you finish this course, you will be able to:

- Define sepsis, severe sepsis, and septic shock.
- Identify the groups of people with the highest risk of developing sepsis.
- Summarize the major factors that coalesce to cause sepsis and list the key events in the systemic spread of a septic reaction.
- Name the important diagnostic signs and laboratory values suggestive of sepsis.
- Discuss shock and its identification in septic patients.
- Explain the four steps in the initial treatment of sepsis.
- Identify the effects on organs and organ systems as management of sepsis continues.
- Explain the scoring systems and other methods for determining a prognosis with sepsis.
- Discuss prevention and treatment optimization efforts as proactive approaches to sepsis.

An Ever-Present Threat

Sepsis [a word] derived from the Greek verb *sepo* (meaning “I rot”), has been recognized for millennia and refers to the disseminated inflammatory response elicited by microbial infections. Despite its ancient etymology, sepsis remains a current challenge: it is increasing in frequency, expensive to treat, and lethal, with an associated rate of death as high as 70%.

Lee and Slutsky, 2010

Sepsis is inflammation that is out of control and ravaging the entire body. Sepsis is triggered by an infection. Most often, the infection is bacterial, but infections of fungi, viruses, and protozoans can also trigger sepsis. The infection can be blood-borne or it can be limited to one small area, but once a septic reaction is triggered, the resulting damage is widespread, extensive, and life threatening.

People who are elderly, immunocompromised, or neutropenic (i.e., who have an abnormally low level of white blood cells) are the most likely to develop a septic response to an infection. Our population is aging and medical care is increasing the longevity of immunocompromised patients, and the number of cases of sepsis continues to increase.

In a classic systemic infection, such as a strep throat, the body's immune response is self-limiting: the immune forces are marshaled, the battle is fought, and the army retires. Sepsis begins like a typical infection, and initially, it often presents with the signs of a classic systemic infection—fever, tachycardia, tachypnea, and an elevated white blood cell count. However, in sepsis, the natural checks and balances have failed. Instead of tapering off and disappearing, the inflammatory forces spread beyond the infected region.

The spread begins as pro-inflammatory signal molecules enter the blood stream in large numbers. As they course through the vascular tree, these molecules damage the endothelium that lines the blood vessels. The orderly passage of gases, nutrients, and fluids through the capillary walls is disrupted, and organs become hypoxic and energy-starved.

If the sepsis continues, organ damage becomes organ failure, and at this point, the condition is called "severe sepsis." Severe sepsis increases the likelihood that the patient will die. Sometimes, the organ-system that fails is the vasculature itself, and the arterial wall muscles can no longer contract sufficiently to maintain adequate blood pressure. Now, the patient is in septic shock, and the patient's chances of surviving decline farther (Shapiro et al., 2010).

The systemic meltdown that occurs in sepsis is a syndrome unto itself. It is called "Systemic Inflammatory Response Syndrome" or "SIRS." SIRS can be triggered by a range of causes, including noninfectious insults, such as pancreatitis, trauma, or burns. When it is triggered by an infection, SIRS is called "sepsis," and, unlike other types of SIRS, sepsis must be treated with antibiotics and with attempts to remove or to control the primary source of the infection.

Appropriate antibiotics are necessary to treat sepsis successfully, but even the correct antibiotics will not stave off the high mortality rates of sepsis if they are given too late. To optimize a patient's chances of survival, sepsis must be treated rapidly and efficiently. Every hour of delay in treatment reduces the average patient's survival by 8%.

Typically, management of sepsis requires a period of critical care in an intensive care unit. Treatment begins with a six-hour window dedicated to infusing large quantities of intravenous fluids, stabilizing ventilation and circulation, beginning diagnostic studies, administering antibiotics, and searching for and then cleaning the infected tissues. When this initial work is done, the patient is given supportive critical care.

The average septic patient spends 2 1/2 to 4 weeks in a hospital. Even with experienced care, approximately 1 in 5 septic patients die. The mortality rate is worse for severe sepsis and for septic shock.

Clinical Definitions

Sepsis is a potentially fatal disease. For the best chances of treating it successfully, clinicians need to recognize it early and treat it quickly but it can be difficult to diagnose, especially early in the course of the disease.

Sepsis coexists with an infection, and often with other diseases, all of which produce their own signs and symptoms. The challenge is to pick out the signs of sepsis from among the other abnormalities plaguing the patient. To make sepsis easier to identify, there has been an effort to standardize its definition despite its wide range of presentations. Following are the current clinical definitions of sepsis and its related terms.

Sepsis is an unchecked whole-body response to an infection, regardless of whether the infection is local, extensive, or blood-borne. This response produces two or more of the signs of Systemic Inflammatory Response Syndrome (SIRS), defined below. The septic reaction threatens to damage distant organs and to destabilize the circulatory system. Sepsis can lead to organ failure, shock, and death.

Systemic inflammatory response syndrome (SIRS) is an inflammatory reaction that produces at least two of the following four signs:

- Abnormal body temperature ($<36^{\circ}\text{C}$ or $>38.3^{\circ}\text{C}$)
- Tachycardia (>90 beats/min)
- Tachypnea (>24 breaths/min or a rate sufficient to produce $\text{PaCO}_2 <32$ mm Hg)
- Abnormal white blood cell count ($>12,000/\text{mm}^3$, $<4000/\text{mm}^3$, or $>10\%$ immature forms)

SIRS due to abnormal white blood cell count ($>12,000/\text{mm}^3$, $<4000/\text{mm}^3$, or $>10\%$ immature forms) can be triggered by an infection, but it can also arise from noninfectious sources, such as trauma, hemorrhage, burns, surgery, adrenal insufficiency, pulmonary embolism, dissecting or ruptured aortic aneurysm, myocardial infarction, occult hemorrhage, cardiac tamponade, post-cardiopulmonary bypass syndrome, autoimmune disorders, pancreatitis, vasculitis, anaphylaxis, or drug overdose (Neviere, 2010a,b). SIRS can lead to organ failure, shock, and death.

Severe sepsis, or “sepsis syndrome,” is present when the patient has progressed to a stage in which organs or organ systems begin to fail.

Severe sepsis is sepsis plus one of the following clinical problems:

- Cardiovascular system dysfunction

- Acute respiratory distress syndrome (ARDS)
- Dysfunction of two or more other organs or systems

Septic shock, in a patient with sepsis, is acute circulatory failure with refractory (difficult to reverse) hypotension that is unexplainable by other causes. The term “shock” describes a condition in which many tissues throughout the body become hypoxic due to poor perfusion. In shock, normal homeostatic mechanisms are either not functioning or not adequate to deliver enough oxygen to tissues. If it is not reversed, shock leads to organ failures and death.

Shock is categorized as:

- Hypovolemic, in which the patient has suffered a large loss of fluid, such as by hemorrhage
- Cardiogenic, in which the heart cannot pump sufficient blood volume, such as after a major myocardial infarction
- Distributive, in which sufficient fluid cannot be kept inside the vasculature, as in anaphylaxis (Gaieski, 2010)

Septic shock is a form of distributive shock. In septic shock, there is hypotension that cannot be reversed by giving adequate fluids. When the hypotension of septic shock also does not respond to vasopressors, the condition is called “refractory septic shock” (Munford and Suffredini, 2009).

Other terms related to sepsis include:

- **Microbial Infection**—growth of nonnative microbes or overgrowth of native microbes in the body
- **Bacteremia**—viable bacteria in the bloodstream
- **Multiple organ dysfunction syndrome (MODS)**—the failure of a number of organs or organ-systems caused by an illness. To be considered “in failure,” an organ must persist in its severe dysfunction for at least 24 hours. As the number of failing organs increases, so does the risk of mortality.
- **Hypotension**—Systolic blood pressure <90 mm Hg. Or mean arterial pressure <60 mm Hg, or drop in systolic blood pressure of >40 mm Hg from the patient's baseline (Dellinger et al., 2008)
- **Mean arterial pressure (MAP)**—an indicator of general tissue perfusion-pressure: At low heart rates, MAP ~1/3 systolic BP + 2/3 diastolic BP; At high heart rates, MAP ~1/2 systolic BP + 1/2 diastolic BP. Normal MAP is 70–110 mm Hg.

Epidemiology of Sepsis

The Big Picture

Severe sepsis is common, expensive, and frequently fatal. More than 750,000 cases of sepsis occur annually in the United States, and its incidence continues to rise. The growth of the number of cases of sepsis has outstripped the growth of the population. Between the late 1970s and today, the American population increased by 35%; in the same period, the number of cases of sepsis increased by more than 350% (CDC, 2010).

The high number of cases of sepsis in the United States is a byproduct of medical advances. The populations most susceptible to sepsis—the elderly, people with chronic diseases, and people with immune-compromising diseases, such as AIDS—are living longer. Two other aspects of modern medicine that increase the risk of sepsis are also on the rise:

- The widespread use of antimicrobial and immunosuppressive drugs
- Devices that are sites for infection, such as indwelling catheters, internal mechanical devices (such as pacemakers), and mechanical ventilation (Munford, 2008)

Sepsis is an especially serious condition. More than half of all patients diagnosed with severe sepsis are treated in an intensive care unit (ICU). In the United States, 2% to 3% of the hospitalized patients have severe sepsis, but those patients account for 20% of the hospitals' ICU admissions (CDC, 2010).

The average sepsis survivor has received between 7 and 14 days of ICU care followed by an additional 10 to 14 days of hospitalization. In 2009 this care cost more than \$22,000 per patient, and nationwide the cost was \$17 billion. The national costs of sepsis are similar to the national costs of ischemic heart disease (coronary artery disease) (CDC, 2010; Lagu et al., 2011).

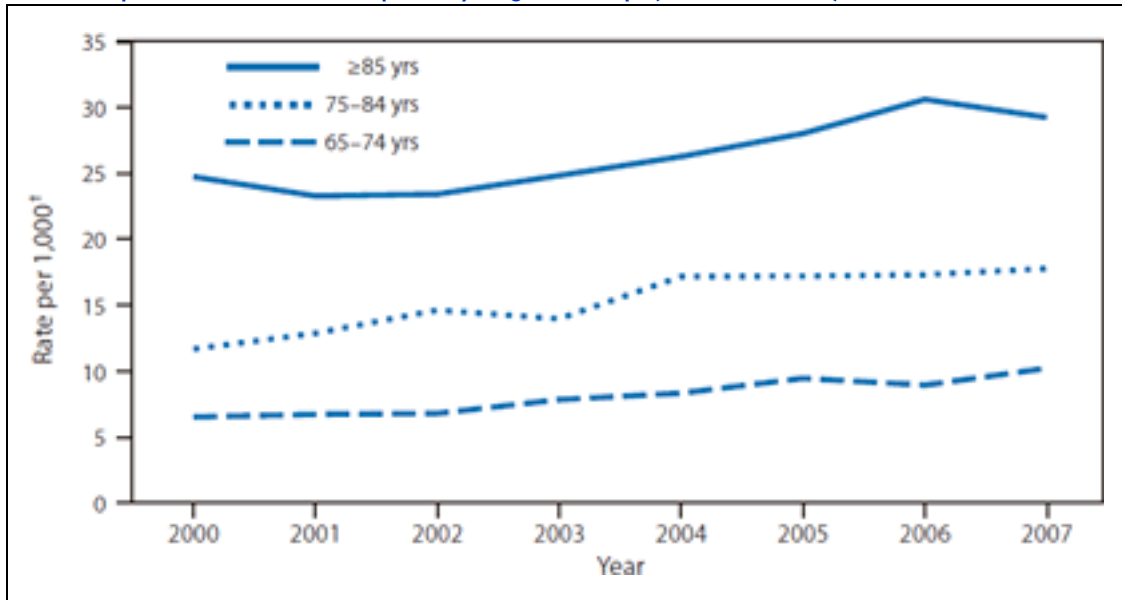
While the number of cases of sepsis is increasing, the mortality rate is declining. Nonetheless, the death rate is still very high. Approximately 1 of every 4 patients with severe sepsis and 1 of every 2 patients with septic shock will die within 30 days of their diagnosis. All told, sepsis contributes to almost 30% of all U.S. deaths and to almost 40% of the deaths of Americans older than 85 years (Munford, 2008; CDC, 2010).

Susceptible Populations

Anyone can get sepsis, but **those who are ill and weakened** are the most vulnerable—about 2 of every 3 patients who develop sepsis already had another significant illness. People with chronic illnesses (eg, diabetes, cancer, kidney disease, liver disease) are at increased risk of developing sepsis, as are those suffering from physical trauma or burns (Munford, 2008). Likewise, patients with weakened immune responses (eg, from chemotherapy, AIDS, long-term steroid use) are more likely to develop sepsis. The risk is also greater for a person with an implanted device, such as an intravascular catheter, a pacemaker, or an endotracheal tube (Neviere, 2010a).

Incidence and mortality from sepsis both increase with the patients' age. Two-thirds of the patients who develop severe sepsis are older than 65 years, and the likelihood of getting sepsis increases dramatically thereafter.

U.S. Hospitalizations for Sepsis by Age Group (2000–2007)



Hospitalizations per 1000 Americans for sepsis in three different age groups, during the years 2000 to 2007. Comparing the three lines, the risk of getting sepsis increases with age: people older than 85 years are 5 times more likely to be hospitalized for sepsis than are people aged 65–74 years. Source: CDC, 2010.

Pathophysiology of Sepsis

Causes of Triggering Infections

The underlying cause of sepsis is microbial. The culprit microbes can be bacteria, fungi, viruses, or protozoans. It is not always possible to identify the microbe that is causing a particular case of sepsis, but when the infectious agent has been discovered, two-thirds of the time the causative microbes have been bacteria (Munford, 2008).

Historically, gram-negative bacteria (*Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Serratia marcescens*, and *Haemophilus* spp.) were the chief triggers of sepsis. Recently, however, gram-positive bacteria (*Staphylococcus aureus*, coagulase-negative staphylococci, enterococci, *Streptococcus pneumoniae*) have taken first place. Among the fungi, *Candida* species are the most common causes of sepsis (Munford and Suffredini, 2009).

The likelihood that a local infection will progress to sepsis varies according to its source tissue. For example, pulmonary or abdominal infections are 8 times more likely to develop into sepsis than are urinary tract infections (Munford, 2008).

Obviously, most infections do not trigger a septic reaction. Two people can have infections in the same tissues and caused by the same microbe, yet one person will develop sepsis and the other person will not. This difference indicates that other factors, beyond the type of tissue and the kind of microbe, are involved in the development of sepsis.

What are these other factors?

One clue is the source of the bacteria that most commonly cause sepsis. Bacteria that cause classic infectious diseases, such as *Neisseria meningitides* (meningitis) or *Streptococcus pyogenes* (strep throat), lead to sepsis less frequently than do bacteria that are considered commensal ("normal flora"), such as *Staphylococcus aureus* or the enterococci. Commensal bacteria are notorious for causing systemic disease in people who have weakened antimicrobial defenses—AIDS patients, immunosuppressed patients, or patients with damaged epithelia or endothelia. The fact that commensal bacteria are also the most common causes of sepsis suggests that sepsis is most readily triggered in people who have weakened antimicrobial defenses.

To develop sepsis, a microbial infection is necessary but not sufficient: it appears that a patient also needs a pre-existing susceptibility. Support for this idea can be seen in large surveys of ICU patients. These surveys found that "approximately 70% to 80% of the cases of severe sepsis in adults occurred in individuals who were already hospitalized for other reasons" (Munford and Suffredini, 2009).

Spread of the Inflammatory Reaction

Normally, an inflammatory reaction remains local. In contrast, the septic reaction uses the vascular system as a highway to spread inflammation system wide. In sepsis, pro-inflammatory molecules can be found in high concentrations throughout the circulation. In addition, activated coagulation factors are found throughout the bloodstream, making the entire vascular tree vulnerable to perfusion-interrupting clots and, in some cases, to disseminated intravascular coagulation (DIC). In many septic infections, bacterial byproducts worsen the condition as they, too, are carried to distant tissues (Munford, 2008).

Pro-Inflammatory Molecules in the Circulation

Three hallmarks of the body's response to infection are the cytokines, activated complement, and activated coagulation factors. All of these factors underlie the process that leads to the presence of sepsis.

Cytokines

One aspect of the body's normal response to infection, and key to the propagation of a septic reaction, are the cytokines. As in the normal response to an infection, the septic reaction begins with inflammatory cells, mainly macrophages in the local tissues and neutrophils in the bloodstream. When the macrophages recognize invading microbes, they react by producing pro-inflammatory molecules called cytokines.

Cytokines

Cytokines are a varied group of signaling molecules used by the immune system. A wide range of cells have the ability to produce cytokines, including dendritic cells, macrophages, mast cells, helper T cells, and endothelial cells. One consequence of the activation of immune cells is the turning on of their cytokine production. Cytokines are produced temporarily, as needed, and they are intended to be fast acting, so they are not stored but are secreted as soon as they are manufactured.

The cytokines include interleukins, interferons, tumor necrosis factor, transforming growth factor, and other lymphokines, chemokines, and growth factors. (A cytokine's name often reflects its particular functions.) In most cases, cytokines act locally, either on the producing cell itself or on neighboring cells. However, when manufactured in large quantities, as in sepsis, cytokines are swept into the circulation and cause trouble in distant parts of the body (Abbas et al., 2011).

Near the infection, neighboring endothelial cells respond to the sudden surge of cytokines by producing adherence molecules. Meanwhile, neutrophils are being attracted from the bloodstream. The neutrophils stick to the activated endothelial cells and then begin to produce even more pro-inflammatory cytokines.

Note: These initial processes take place in all infections—typical infections and those destined to turn septic.

Activated Complement

A second aspect of the body's normal response to infection is the triggering of the complement system. The complement system is a sequential set (a cascade) of protein activations that helps to immobilize and break down pathogens. When activated, the complement proteins identify and label foreign molecules. Some complement components lyse membranes of foreign cells. In addition, activated complement proteins multiply the effects of the local immune reactions by putting yet more cytokines into play (Neviere, 2010a).

Activated Coagulation Factors

A third hallmark of the normal inflammatory response to an infection is the local activation of the blood coagulation system. This leads to the deposition of fibrin by the coagulation cascade in a sticky meshwork then helps to fence in and restrict the spread of microbes from the vicinity.

A consequence of the coagulation reactions is the activation of bradykinin. **Bradykinin** is a circulating peptide that dilates blood vessels and makes capillaries leaky. An increase in the local concentration of bradykinin adds to the vasodilation and capillary leakage that is being caused by histamine and prostaglandins. (Histamine is released by mast cells in response to the activation of complement proteins, and prostaglandins are released by activated neutrophils, mast cells, and endothelial cells.) As a result, local tissues begin to swell with a protein-rich edema fluid (Neviere, 2010a).

Weakened Inflammation Control Mechanisms

Sepsis begins as the typical inflammatory response to an infection. Like any inflammation, it starts with the local mobilization of macrophages and neutrophils and the activation of the complement and coagulation systems. An array of pro-inflammatory cytokines is produced, and there is local edema.

At this point, however, the septic reaction diverges from the body's usual reaction, because in sepsis, the final half of the typical inflammatory response—the winding down and ending—never happens. According to Nevriere (2010a),

Sepsis has been referred to as a process of malignant intravascular inflammation. It is considered malignant because it is uncontrolled, unregulated, and self-sustaining. It is considered intravascular because it represents the blood-borne spread of what is usually a cell-to-cell interaction in the interstitial space. It is considered inflammatory because all characteristics of the septic response are exaggerations of the normal inflammatory response.

A Typical Inflammatory Reaction

. . . the body's systemic responses to injury and infection normally prevent inflammation within organs distant from a site of infection.

Munford, 2008

When working properly, the innate immune mechanisms are rapidly mobilized in the region of a new infection. At the height of the response, invading microbes are overwhelmed, deactivated, and destroyed. Next, local debris is removed; the pro-inflammatory molecules, the activated complement, and the activated clotting factors are neutralized; and the production of new pro-inflammatory molecules stops. In other words, a typical inflammatory response has a rising phase leading to local activity; the local activity then automatically tapers off and ends.

The inflammatory response must be terminated because it is imprecise and it causes collateral damage: it injures or destroys nearby tissues as well as the invading microbes. Therefore, in a typical inflammatory reaction, when the local attack is over, the activated cells and molecules are neutralized by a wave of deactivation molecules.

Deactivators are produced as normal components of the clean-up operation. Within cells, suppressor factors decrease the manufacture and secretion of pro-inflammatory cytokines. At the same time, outside the cells, a newly secreted class of anti-inflammatory cytokines opposes the activated pro-inflammatory molecules. In addition, specific restorative compounds (lipoxins, resolvins, and protectins) are secreted to stabilize and encourage the repair of local cells.

The typical response to an infection includes other protective mechanisms. To shield distant tissues from the unavoidable destruction caused by immune reactions, the local pro-inflammatory response sets off counterbalancing systemic anti-inflammatory responses. For example, local infections lead to an increased systemic circulation of cortisol, epinephrine, prostaglandins, and many proteases, all of which inhibit immune reactions throughout the body.

An Atypical Inflammatory Reaction

In a typical inflammatory reaction, the local pro-inflammatory processes are balanced by systemic anti-inflammatory processes and are automatically terminated within a short time. In sepsis, however, cytokine production continues unending and the circulatory spread of the cytokines then causes increased cytokine production at distant sites.

Sepsis is an atypical inflammatory reaction in which the pro- and anti-inflammatory balance is off kilter, with the pro-inflammatory processes dominating.

A well-studied example is the amount of protein C in the blood. One of the anticoagulation pathways that normally keep the coagulation system under control depends on the availability of sufficient activated protein C. A characteristic of patients with sepsis is that they have an unusually low level of activated protein C in their circulation. This deficit allows the coagulation system to deposit fibrin widely, making it more likely that small clots will form throughout the vascular tree (Shapiro et al., 2010).

Protein C

Protein C—a different molecule from C-reactive protein, CRP—is a circulating enzyme that is made in the liver. When activated, protein C blocks two coagulation factors, making clotting less efficient. Activated protein C also promotes the dissolution of clots (fibrinolysis). Beyond its antithrombotic functions, activated protein C acts on endothelial cells to reduce their sensitivity to pro-inflammatory molecules and to enhance the endothelial cells' normal function as barriers between the blood and the tissues (Bauer, 2010).

If unopposed by protein C—dependent blockades, the continuous stimulation of the coagulation system will sometimes lead to "disseminated intravascular coagulation (DIC), with eventual clot formation, impaired tissue perfusion, and thrombosis of small vessels. These events intensify the inflammatory response, and a vicious cycle occurs" (Jui, 2010).

Many checks and balances keep a typical inflammatory response local. In a patient who develops sepsis, some of these restrains have been weakened. This allows a wave of destructive inflammation to wash through the vasculature of the whole body. Whether an infection turns septic is determined more by the body's ability to control inflammatory reactions than by the particular organism causing the infection (Neviere, 2010a).

Inflammatory Effects of Particular Molecules

In certain cases of sepsis, there is an additional force contributing to the system-wide spread of inflammation. Molecules produced by some microbes accelerate the septic reaction, making it especially rapid and severe (Neviere, 2010a).

Classic examples are the bacterial toxins:

- **Endotoxin** is a lipopolysaccharide in the cell wall of gram-negative bacteria. When it gets into the circulation, endotoxin strongly activates the coagulation and complement systems throughout the body.
- **Exotoxins** are another class of sepsis-worsening molecules that are produced by gram-positive bacteria. Exotoxins are superantigens, meaning that they bypass the standard immune activation process and directly trigger host cells to pour out cytokines. This happens in toxic shock syndrome, a form of septic shock in which staphylococcal exotoxins have gotten into the patient's circulation and triggered a rapidly progressing and debilitating sepsis. (See Toxic Shock Syndrome below.)

Effects of the Spreading Inflammatory Reaction

Endothelial Damage

The endothelial cells that line blood vessels are the gatekeepers between the bloodstream and the body's tissues. A normal inflammatory reaction activates local endothelial cells but it also damages those same cells. Sepsis multiplies this effect by activating and damaging endothelial cells in patches throughout the entire vascular tree. In sepsis there are many places in the body where the barrier between the bloodstream and the surrounding tissues has become leaky and crowded with immune cells (Ely and Goyette, 2005).

Organ Damage

Damage to the vascular endothelium causes both edema and the collection of neutrophils and macrophages. In damaged regions, gas exchange is reduced, nutrients cannot diffuse into the tissues, and waste products cannot diffuse out. An organ with significant damage to its vascular endothelium ends up poorly perfused and ischemic. Such an organ will function poorly (organ dysfunction), or it will fail altogether. As sepsis continues, it causes increasing organ dysfunction and then organ failures, and the risk of the patient dying doubles for each organ that fails (Shapiro et al., 2010).

Lungs

The lung is usually an early casualty in sepsis, regardless of the location of the initial infection. The surface area of the vascular endothelium of the lung is large, and when a septic reaction begins disrupting endothelial areas haphazardly in the body, the lung is likely to suffer significant damage.

Regions of the lung with damaged endothelia become filled with neutrophils and macrophages. Interstitial spaces develop edema, fibrin is deposited, and surfactant is reduced. These regions of the lung become heavy and poorly compliant and local gas exchange is minimal.

To make matters worse, the phenomenon of hypoxic pulmonary vasoconstriction (HPV) is counteracted in sepsis. HPV is a protective mechanism that normally redirects arterial blood away from any nonfunctioning parts of the lung (Aronson, 2005). In sepsis, however, circulating inflammatory molecules reduce the ability of lung arterioles to constrict. Without HPV, blood will continue to flow through useless regions of the lung, and the body's growing systemic hypoxemia worsens (Neviere, 2010a).

Increasing lung dysfunction eventually leads to lung failure. In sepsis, lung failure takes the form of acute respiratory distress syndrome, or ARDS.

Acute Respiratory Distress Syndrome (ARDS)

Acute respiratory distress syndrome is sudden-onset pulmonary edema caused by endothelial injury in the lungs. Other causes, such as cardiac failure or pneumonia, can produce pulmonary edema, but in ARDS, the edema occurs as a direct result of lung injury.

During ARDS, leaky pulmonary capillaries allow alveoli to be flooded, and the lungs get heavy and are poorly compliant. Chest films of ARDS patients show diffuse or patchy infiltrates bilaterally. Gas exchange is reduced, and the patient becomes dyspneic and hypoxemic.

One characteristic of the hypoxemia in ARDS is a low arterial oxygen level that remains low at all levels of oxygen supplementation. In other words, the ratio of the concentration of the arterial O_2 to the concentration of the inspired O_2 remains below 200— $PaO_2/FiO_2 < 200$ (Jui, 2010). Management of ARDS includes mechanical ventilation, treatment of the cause of the lung injury, and supportive care (Jui, 2010).

ARDS comes on quickly; it can appear in minutes to hours after the onset of sepsis. The condition presents as the sudden appearance of severe refractory hypoxemia. The lungs become fluid-filled and poorly compliant, and the patient is in distress. An emergency chest film shows new bilateral diffuse or patchy pulmonary infiltrates, and mechanical ventilation is usually required (Jui, 2010).

Sepsis is the most frequent cause of ARDS, and ARDS develops in approximately half of all patients with severe sepsis or septic shock. On average, ARDS has a mortality rate of 30% to 40%, but in sepsis, ARDS has a mortality rate $>50\%$.

Heart

In a patient without pre-existing cardiac problems, the heart frequently weathers a bout of sepsis. From the beginning, sepsis causes leaky capillaries, which reduces blood volume and lowers blood pressure. At first, the vascular system responds with arterial constriction and increased vascular tone. This helps the heart to maintain a normal cardiac output. (See Clinical Assessment of Cardiac Output, below.)

As the sepsis continues, the heart muscle begins to weaken, due to the depressant effect of some of the circulating inflammatory molecules. However, the weakened ventricles also stretch, so the dilated ventricles pump extra blood with each stroke. The additional stroke volume partially compensates for the heart's decreased pumping power. In this way, the cardiac output (blood volume pumped per minute) can remain fairly constant or can even increase during a bout of sepsis.

Kidneys

Like the lung, the kidney's function is entirely dependent on maintaining a significant area of intact vascular endothelium. When the septic reaction invades the kidneys, neutrophils and macrophages begin to fill the interstitial tissue, and the endothelial cells of the blood vessels are activated and damaged. At the same time, the kidneys, indeed all body tissues, become underperfused and hypoxic.

At first, kidney dysfunction appears as a reduced glomerular filtration rate and an increase in serum creatinine levels. If the sepsis continues, acute tubular necrosis develops and eventually this can lead to acute renal failure (Neviere, 2010a).

Gastrointestinal Tract

The spreading hypoperfusion of sepsis limits the oxygen supply to the intestines. As aerobic metabolism is superseded by anaerobic metabolism, lactate levels build in the portal vessels, and the pH drops inside the gut.

Hypoxia and acidosis stress the epithelium that lines the gastrointestinal tract, and its natural barrier functions (including protection against gut microbes) are weakened. Bacteria and toxic molecules from the gut lumen slip through the gut wall and into the bloodstream and the lymphatics.

Sepsis typically causes small painless erosions in the mucosa (especially in the upper GI tract), resulting in a continual seepage of blood. In severe sepsis or septic shock, the hypoperfusion can also immobilize the intestines, which develop paralytic ileus (Neviere, 2010a).

Liver

No organ escapes the effects of sepsis. The flood of circulating inflammatory mediators soon switches hepatocyte metabolism toward gluconeogenesis, amino acid uptake, and protein synthesis. At the same time, however, hypoperfusion uniformly decreases all the liver functions; this reduces the liver's ability to help to clear bacteria, bacterial toxins, and debris from the circulation (Ely and Goyette, 2005).

Nervous System

A long list of dysfunctions plagues the nervous system of a patient with severe sepsis. The problems begin when circulating inflammatory molecules disrupt the endothelium of the blood vessels along the blood-brain barrier. The leaky blood-brain barrier lets inflammatory molecules, along with infiltrating white cells, into the neural tissue. Subsequently, edema and collections of cells around arterioles hinder the entry of oxygen and nutrients and the exit of metabolic wastes. In this milieu, neurons shut down and cerebral functions slow.

Among the other neural problems, septic patients can develop a long-lasting peripheral neuropathy that is similar to the neuropathy seen in other critical illnesses (Ely and Goyette, 2005).

Progression to Shock

Severe sepsis occurs when organ dysfunction progresses to organ failure. If arteries fail to constrict, septic shock occurs. In septic shock, episodes of hypotension cannot be reversed by giving more fluids.

Severe sepsis often progresses to shock. Of every 4 patients who are not in shock when they present to the emergency department with sepsis, 1 patient will develop shock within 72 hours, even after having received appropriate and timely antibiotic therapy (Glickman et al., 2010).

In septic shock, blood vessels can no longer constrict sufficiently to maintain an adequate blood pressure. Three processes contribute to the unresponsiveness of the arterial wall muscles in septic shock:

- High levels of lactic acid hyperpolarize the arterial muscle cells, making them unable to respond when stimulated.
- Sepsis suppresses the release of vasopressin (ADH), a pituitary hormone that, among other functions, maintains arterial wall muscle tone.
- Sepsis causes endothelial cells to produce excess nitric oxide, which is a vasodilator. (Shapiro et al., 2010)

Progression to Death

There are remarkably few published data regarding the processes leading to death in critically ill patients in general and particularly in septic patients.

Vincent et al., 2011

The best available information suggests that death in sepsis most often results from the irreversible failure of a number of organ systems rather than from the failure of any one particular organ or system. However, in those cases where death can be attributed to the failure of a single system, it is usually the cardiovascular, respiratory, or central nervous system (Vincent et al., 2011).

Diagnosis of Sepsis

The rapid diagnosis of sepsis is critical for its successful treatment, but diagnosing sepsis can be difficult. On paper, recognizing a septic patient can seem straightforward. Septic patients have an underlying infection with a systemic response. Septic patients should look ill and should have the classic signs of a systemic infection:

- Fever
- Tachypnea
- Tachycardia
- High white blood cell count

The severity of the septic reaction should also produce other warning signs, such as:

- Hot, flushed skin
- Newly altered mental status
- Hypotension
- Widened pulse pressure (Pulse pressure is the difference between the systolic and the diastolic blood pressure values.)
- Elevated blood lactate level
- Thrombocytopenia

One difficulty in using these signs to recognize sepsis is that the signs are nonspecific: each sign can be produced by a wide range of causes.

A second difficulty is that septic patients do not always present with the same list of signs. For example, a significant number—one study found 40%—of septic patients have a normal rate of respiration. Some septic patients—notably, the very young, the elderly, and the immunocompromised—present with no fever. Moreover, in some septic patients with an underlying infection, blood cultures are negative for microbes.

Despite a great many clinical studies of septic patients, none have found an individual robust test for sepsis. Likewise, no single list of signs, symptoms, and test values has been discovered that can faithfully identify the condition, especially early on.

Most often, the diagnosis of sepsis is made based on clinical experience: physicians recognize clusters of signs and measurements that, while individually nonspecific, together point to sepsis. The diagnostic clusters are drawn from the full range of medical analyses, using history, physical examination, measures of cardiac and renal functioning, and lab studies (see Clinical Signs of Sepsis). Because there is pressure to diagnosis sepsis rapidly, this full gamut of medical data must be collected quickly and analyzed efficiently (see box) (Glickman et al., 2010).

Clinical Signs of Sepsis

A septic patient has an infection and a number of the following signs.

- Appearance
 - Acutely altered mental status
 - Edema
 - Looks ill
- Vital signs
 - Abnormal body temperature: fever ($>38.3^{\circ}\text{C}$) or hypothermia ($<36^{\circ}\text{C}$)
 - Hypotension: systolic BP <90 mm Hg or mean arterial pressure <70 mm Hg or a drop in systolic BP >40 mm Hg or the need for vasoactive drugs to maintain normal BP
 - Tachycardia (>90 beats/min)
 - Tachypnea (>30 breaths/min)
- Blood chemistries
 - High blood level of C-reactive protein (CRP) (>2 std. dev. above normal)
 - High blood level of procalcitonin (>2 std. dev. above normal)
 - Hyperbilirubinemia (plasma total bilirubin >4 mg/dl [normal: 0.1–1.0 mg/dl])
 - Hyperglycemia (blood glucose >140 mg/dl) with no history of diabetes
 - Hyperlactatemia (lactate >3 mmol/l [normal: 0.5–2.2 mmol/l])
 - Unexplained base deficit >5.0 mEq/l [normal: <3.0 mEq/l]
- Blood gases
 - Hypercapnia ($\text{PaCO}_2 >65$ mm Hg [normal: 33–44 mm Hg] or $\text{PaCO}_2 >20$ mm Hg above patient's baseline)
 - Hypoxemia ($\text{PaO}_2/\text{FIO}_2 <300$ or mixed venous oxygen saturation (SvO_2) $<70\%$ [normal: $\sim 75\%$])
- Blood components
 - Abnormal white blood cell count (WBC)
 - Leukocytosis (WBC count $>12,000$ / mm^3 [normal: 4,500–11,000 / mm^3]) **or**
 - Leukopenia (WBC count <4000 / mm^3 [normal: 4,500–11,000 / mm^3]) **or**
 - Normal WBC count with $>10\%$ immature forms [normal: 3%–5%]
 - Coagulation dysfunction (INR >1.5 [normal: 0.9–1.2] or activated partial thromboplastin time >60 s [normal: 30–42s])
 - Thrombocytopenia (platelet count $<100,000$ / mm^3 [normal: 150,000–400,000 / mm^3] or a drop of 50% in platelet count from patient's high in past 3 d)
- Heart function
 - Increased capillary refill time (>2 s)
 - Mottled skin
- GI function
 - No bowel sounds (paralytic ileus)

- Kidney function
 - Increasing blood levels of creatinine (≥ 0.5 mg/dl above patient's baseline)
 - Low urine output (< 0.5 ml/kg/h) despite adequate fluid administration

Source: Jui, 2010; Gutovitz et al., 2011.

Clinical Signs

Potential clinical signs of sepsis are listed in the preceding table. The following sections give details, nuances, and qualifiers of some of some key signs.

Vital Signs

Temperature

Septic patients often have a fever, sometimes with chills and sometimes with an abrupt onset. However, the majority of septic patients are elders, and this demographic brings with it a qualifier about using fever to recognize sepsis. Elder patients develop fevers less readily than younger patients, and sepsis in elders can present without fever, with only a modest fever, or with hypothermia. (When an elder does present with a fever, the underlying illness tends to be more severe.) Other groups that are less likely to have a significant fever with sepsis are patients in renal failure and patients taking high doses of corticosteroids (Jui, 2010).

Tissue need for oxygen increases in a person with a fever, and this worsens the hypoxemia that organs are experiencing in sepsis. Septic patients who present with fevers are more likely than those without fevers to develop shock within the next 72 hours (Glickman et al., 2010).

Heart Rate and Respiratory Rate

Septic patients often have an increased heart rate and an increased respiratory rate. Tachypnea can be one of the first indicators of developing sepsis, and it may be the only sign of an early pneumonia (Ely and Goyette, 2005).

Blood Pressure

Hypotension is a serious sign in sepsis. In general, hypotension can be caused by a decrease in blood volume, a decrease in vascular tone, or a decrease in cardiac output; the hypotension of sepsis can be caused by reductions in all three parameters. Initially, sepsis usually reduces blood volume by increasing capillary leakage, so the administration of fluids is an early priority during treatment (Munford, 2008).

In *sepsis*, the blood volume is not only reduced, it is redistributed ineffectively. Fluid resuscitation will usually refill the under-perfused arteries.

In *septic shock*, poor vascular tone has been added to the patient's other systemic problems. In shock, the administration of large amounts of fluids will not succeed in restoring normal blood pressure (Ely and Goyette, 2005).

Pulmonary

The spread of inflammatory mediators to the lung damages the vascular endothelium and the alveolar capillaries become leaky. This leads to edema, poor lung compliance, and decreased oxygenation of the blood. Thus, septic patients often have tachypnea, labored breathing, crackles on auscultation, hypoxemia, and hypercapnia. If acute respiratory distress syndrome (ARDS) develops, a chest film usually shows diffuse bilateral pulmonary infiltrates.

Cardiac

In a septic patient who does not have a history of major heart problems, cardiac output (the volume of blood pumped by the left ventricle per minute) can remain fairly constant. The cumulative effects of the septic reaction begin to reduce the heart's pumping power; nonetheless, the heart can often increase its output. This comes about because the ventricles dilate as the heart's pumping force declines.

With expanded ventricles, each contraction expels more blood than normal. The increased cardiac output persists even when septic shock sets in. "Increased cardiac output and decreased systemic vascular resistance distinguish septic shock from cardiogenic, extracardiac obstructive, and hypovolemic shock" (Munford, 2008).

Clinical Assessment of Cardiac Output

Cardiac output is the volume of blood that the heart pumps per minute. When initially assessing any seriously ill hypotensive patient, it is important to know whether the patient's cardiac output is adequate.

Clinically, a reduced cardiac output will produce:

- Narrow pulse pressure
- Cool extremities
- Weak pulse
- Delayed capillary refill

An increased cardiac output will produce:

- Widened pulse pressure
- Warm extremities
- Bounding pulse
- Rapid capillary refill

The classic presentation of sepsis includes an increased cardiac output. In early sepsis, hypotension is typically due to loss of intravascular volume, not to decreased cardiac output. When septic shock sets in, it is usually an extracardiac problem; specifically, the vasculature has lost the ability to maintain its tone by responsive arterial constriction. A primary reduction in cardiac output is uncommon in any form of sepsis.

Source: Kress and Hall, 2008.

Much of the cardiovascular dysfunction caused by sepsis is reversible. The cardiovascular system is typically functioning normally again within 10 days of a patient's recovery from an episode of sepsis (Shapiro et al., 2010).

Neurologic

Brain dysfunction in patients with severe sepsis is called "septic encephalopathy." This condition manifests as a change in mental status, with disorientation, confusion, agitation, lethargy, or coma; focal or unilateral neurologic signs are uncommon in septic encephalopathy. Reports of its frequency range widely: from 10% to 70% of septic patients have been reported to develop this neurologic condition (Jui, 2010).

Finally, a full serum chemistry and urinalysis should be done. Values that are often abnormal in sepsis are listed in the Clinical Signs of Sepsis table above.

Hematologic Signs

Blood work for a suspected case of sepsis includes a complete blood count, a platelet count, and a DIC panel (prothrombin time, activated partial thromboplastin time, and the serum concentrations of fibrinogen, D-dimer, and antithrombin III) (Jui, 2010).

Red Blood Cells

Poor tissue perfusion is a critical problem in sepsis. To have an adequate oxygen carrying capacity, a patient needs a sufficient quantity of red blood cells. In sepsis, the initial treatment goals include maintaining a hematocrit $>30\%$ and a hemoglobin concentration >10 g/dl. The septic patient's hematocrit and hemoglobin concentration will vary as fluids shift between compartments in the body, but over time these red blood cell values will drift lower because red cell production and survival times decrease during sepsis.

Complications, such as bleeding or hemolysis (as occurs in clostridial infections), can cause acute drops in the hematocrit (Shapiro et al., 2010).

Oxygen carrying capacity lessens during sepsis for an additional reason. Sepsis causes changes in the body's iron metabolism, so that less than the normal amount of iron is transferred into forming red blood cells (Jui, 2010).

White Blood Cells

Sepsis usually produces an elevated white blood cell count, with an increased number of neutrophils and an increased percentage of immature forms (ie, a left shift or bandemia) (Munford, 2008).

The absence of an elevation of the white blood cell count does not rule out sepsis. Some septic patients develop an abnormally low white blood cell count (leukopenia). Leukopenia with a fever is a particularly worrisome combination and increases the risk of a fatal outcome (Shapiro et al., 2010).

Platelets, Coagulation Factors, and Protein C

Approximately half of all patients with sepsis have low platelet counts (thrombocytopenia). As the sepsis worsens, platelet counts will continue to drop.

Approximately 10% of septic patients have other coagulation abnormalities. There can be:

- Increased prothrombin or activated partial thromboplastin times **or**
- Decreased levels of fibrinogen or antithrombin iii **or**
- Increased levels of fibrin monomer, fibrin split products, or D-dimer (Jui, 2010)

When a septic patient has a combination of coagulation abnormalities, the risk of DIC is increased. DIC occurs in 2% to 3% of septic patients and more frequently in patients with septic shock. Gram-negative bacterial infections trigger DIC more readily than do gram-positive infections (Munford, 2008).

Protein C is a natural anticoagulant factor that helps to counteract the coagulation cascade. (See Protein C, above.) A low blood concentration of activated protein C is typical of sepsis, because the cytokines that are released in the inflammatory barrage of sepsis make it more difficult for protein C to be activated. Decreased levels of activated protein C in the circulation are associated with thrombi, microthrombi, and fibrin deposition in septic patients (Shapiro et al., 2010).

Microbiologic Analysis

Sepsis can be triggered by an infection of any type of microbe. Sepsis is a system-wide reaction, but it can occur even when the microbes are localized and have not invaded the bloodstream. Blood cultures will be negative (ie, they will not find bacteria or fungi) in approximately 2 in 5 cases of septic shock, 3 in 5 cases of severe sepsis, and 4 in 5 cases of sepsis (Kibe et al., 2011). In those cases in which microbes are detected in a septic patient's blood, ~70% of the microbes found are bacteria.

In spite of the many negative results, cultures of the bloodstream and all other potentially infected sites should be taken and sent immediately to a microbiology lab. (See Begin Identifying the Infection, below.) A successful identification of the microbe will eventually allow the optimal antibiotic to be given.

It can take days to receive microbiologic culture results, and successful resolution of sepsis requires the early administration of antibiotics. Therefore, as soon as culture samples have been taken, patients are started on an empiric regimen of antibiotics, with the plan of reassessing the regimen daily.

Direct Laboratory Identification

Not all patients with sepsis-like symptoms have an infection. The same reaction, SIRS, can be triggered by noninfectious causes, and in such cases it is risky to expose the patient to unnecessary antibiotics. For decades, scientists have been trying to find a rapid lab test that will give a quick and reliable diagnosis of sepsis. This has been a disappointing quest: "the search for a highly accurate biomarker of sepsis has become one of the holy grails of medicine" (Kibe et al., 2011).

Sepsis is a complex syndrome. It produces a great many changes in the body's chemistry, and each of these changes is a potential marker for the disease. To date, however, no single physiologic change has been found to be a specific and sensitive identifier for sepsis. Among the many molecules being studied, three that appear to be the most useful are C-reactive protein, complement C3a, and procalcitonin.

An elevated level of C-reactive protein (CRP), a different molecule from protein C, is a useful marker for systemic inflammation in general. In patients with sepsis, CRP levels rise rapidly, mirroring the course of the infection (Ely and Goyette, 2005); however, the rise is not specific to sepsis.

Systemic infections raise the levels of molecules in the complement cascade. One of these molecules, C3a, has proved to be a sensitive and specific marker that can distinguish sepsis from similar-looking cases of noninfectious SIRS (Ely and Goyette, 2005).

An elevated level of procalcitonin (the precursor molecule to the hormone calcitonin) will also distinguish sepsis from noninfectious SIRS. A useful feature of procalcitonin is that its blood levels are good reflections of the severity of a patient's sepsis (Kibe et al., 2011).

Differential Diagnosis

At times the diagnosis of sepsis is straightforward. A patient can present with tachycardia, hypotension, tachypnea, fever, leukocytosis, metabolic acidosis, and complaints attributable to a serious infection such as pneumonia, acute pyelonephritis, or acute peritonitis.

At other times, however, sepsis presents with only a few classic symptoms. This is especially true in the early stages of the disease when the patient may not yet look severely ill and the underlying infection may not be obvious.

Another confusing initial presentation occurs in the patient with sepsis who has acute and dramatic dysfunction of an organ. This draws the physician's attention to that organ and away from the systemic cause for the organ failure.

There can also be diagnostic difficulties when a patient presents with a heterogeneous mix of complaints. Sepsis tends to take hold in patients who already have illnesses, injuries, or infirmities. In these cases, to identify sepsis the clinician must recognize its symptoms amidst the signs and symptoms of the patient's other problems.

For these reasons, the differential diagnosis for sepsis is broad. The accompanying list shows the range of other conditions to consider when attempting to diagnose a sepsis-like condition.

Differential Diagnosis for Sepsis

- Anaphylaxis
- Cardiac
 - Cardiac contusion
 - Congestive heart failure
- Endocrine
 - Adrenal dysfunction
 - Diabetic ketoacidosis
 - Hyperthyroidism
- Metabolic disturbance
- Neurologic
 - Hypothalamic brain injury

- Pancreatitis
- Respiratory
 - Acute respiratory distress syndrome (ARDS)
 - Hypoxia
- Toxic
 - Drug misuse/overdose
 - Neuroleptic malignant syndrome
 - Poisoning
- Trauma/Burn
- Vascular
 - Anemia
 - Dehydration
 - Disseminated intravascular coagulation (DIC)
 - Hemorrhage
 - Vasculitis (Shapiro et al., 2010)

Diagnosis of Septic Shock

A patient who might be in septic shock needs a rapid assessment to exclude other major classes of shock, such as cardiogenic (from myocardial infarction or ventricular arrhythmias), hypovolemic (from hemorrhage or dehydration), or anaphylactic. Then, resuscitation should be the first response.

Presentation

Shock presents with hypotension, oliguria, abnormal mental status (restlessness, confusion, lethargy, or coma), and metabolic acidosis due to an increased concentration of lactate in the blood. When the shock is septic, it can also have tachycardia, tachypnea, fever, and a high white blood cell count (Gaieski, 2010).

The hypotension of shock may be absolute, with a systolic blood pressure <90 mm Hg. Alternately, the hypotension of shock may be relative and take the form of a drop in systolic blood pressure >40 mm Hg; in this situation, hypertensive people can be in shock although their presenting blood pressures are within the normal range. When a person is in shock, vasopressors are frequently needed to maintain adequate perfusion of tissues.

For a patient in shock, diagnostic tests, a physical examination, and a medical history should not delay procedures that will stabilize the patient's circulation and respiration. Instead, data should be collected while the patient is being resuscitated. It is important to know the patient's blood and serum chemistry values, so resuscitators need to draw blood samples.

Initial tests include a complete blood count with a differential, basic blood chemistries, liver function tests, coagulation studies, cardiac enzymes, blood gases, lactate levels, blood type with cross match, and toxicology screening (Shapiro et al., 2010).

Toxic Shock Syndrome

Toxic shock syndrome is a rapid-onset form of septic shock that presents with fever, hypotension, rash, vomiting, and diarrhea. It was first associated with infections of high-absorbency menstrual tampons; now it is recognized as originating from a variety of sources including sino-nasal surgical packing, peritoneal dialysis catheters, intravenous drug injections, and burn wounds. Fatality rates of 15% have been reported. Toxic shock syndrome is usually caused by *Staphylococcus aureus*; a related condition, toxic shock–like syndrome, is usually caused by *Streptococcus pyogenes*.

Toxic shock syndrome is triggered by bacterial toxins rather than by an overwhelming invasion of bacteria, and blood cultures are typically negative. Staphylococci produce exotoxins, compounds that act as superantigens and that trigger inflammation directly without an intervening chain of immune cell activations. The exotoxins circulate in the bloodstream and set off inflammation throughout the body, activating and damaging the vascular endothelium of many tissues. As with all sepsis, when toxic shock syndrome leads to organ failure, the chance of mortality is high (Schwartz, 2010).

Differential Diagnosis

For septic shock, the differential diagnosis should consider a different list of primary conditions than for sepsis without shock. The accompanying list shows the range of serious problems to consider when a septic shock–like condition is being diagnosed.

Differential Diagnosis for Septic Shock

- Acute blood loss
- Adrenal insufficiency
- Anaphylaxis and anaphylactoid reactions
- Cardiac arrest followed by post-resuscitation syndrome
- Cardiogenic shock
- Hypovolemic shock
- Myocardial infarction
- Myxedema coma
- Neurogenic shock after an injury
- Paralysis
- Pericardial tamponade
- Post cardiopulmonary bypass syndrome
- Pulmonary embolus
- Severe dehydration
- Tension pneumothorax
- Thyroid storm
- Transfusion reactions
- Vasogenic shock (Gaieski, 2010)

Initial Treatment of Sepsis

As is true everywhere in medicine, experienced healthcare workers have the most success in treating sepsis. In this case, the healthcare team needs training and practice in the care of critically ill patients. An ICU is usually the appropriate place for a patient with sepsis.

Step One: Resuscitate the Patient

The first six hours are the critical period in the treatment of sepsis. Clinical studies have demonstrated that, during this initial phase, the use of a standardized protocol leads to the fewest mortalities and the shortest ICU stays. The recommended protocol sets specific target values of critical physiologic parameters toward which the treatment procedures aim. This type of management is called **early goal-directed therapy (EGDT)** (Gutovitz et al., 2011).

The basic EGDT protocol for sepsis is published as the *Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock* (Dellinger et al., 2008). In addition to initial treatment procedures and targets, the guidelines give recommendations for managing the later phases of sepsis. The sepsis guidelines assume that all recommendations will be overseen and tailored to the individual patient by an experienced critical care physician.

Targets for Resuscitation of Patients with Sepsis

- Central venous pressure = 8–12 mm Hg (on mechanical ventilation the pressure should be higher, ie, 12–15 mm Hg)
- Mean arterial pressure >65 mm Hg
- Urine output >0.5 ml/kg/h
- Central venous O₂ saturation >70% or mixed venous O₂ saturation >65%
- Hematocrit >30% (Dellinger et al., 2008)

Recommendations

Initially:

- Begin resuscitation as soon as possible.
- Admit the patient to an ICU. If the patient is hypotensive (mean arterial blood pressure ≤65 mm Hg) or if the blood lactate level is elevated (≥4.0 mmol/l), begin resuscitation immediately if any delay in getting to an ICU.

Respiration

The first priority when treating a critical illness is to ensure a patent airway and adequate ventilation. If the venous oxygen saturation target is not met, provide supplemental oxygen or begin mechanical ventilation. There are many reasons that a septic patient might need mechanical ventilation from the outset. A patient who is in shock may be obtunded (have less than full mental capacity) or unconscious and need to be intubated. A septic patient may have pneumonia or ARDS, or, lactic acidosis or pulmonary edema may have significantly increased the work required by the respiratory muscles.

Blood Volume

Typically, a septic patient is hypovolemic. Therefore, with any suggestion of poor tissue perfusion, intravenous fluids are begun—either colloids or crystalloids will work. Severe sepsis or shock may require large volumes of fluid infusion: one study found that an average of 5 liters of crystalloid was necessary in the first 6 hours.

Fluid is given in boluses (eg, 500 ml of a crystalloid) every 5 to 10 minute, with blood pressure, tissue perfusion, and pulmonary edema assessed before and after the bolus. Fluids are administered until the target values are met, initially aiming for a central venous pressure of 8 mm Hg (12 mm Hg in mechanically ventilated patients). Fluids are stopped if pulmonary edema develops or when no improvement in the target values is seen. As always, an experienced critical care physician should individualize the specifics of each patient's treatment.

Blood Components

The International *Guidelines* suggest that septic patients with hematocrits below 30% should receive a transfusion of packed red blood cells. After the resuscitation phase of treatment, and when tissue perfusion has improved, the target for transfusion is a hemoglobin concentration of 7.0 g/dl or better. However, there is uncertainty about these transfusion recommendations (Munford, 2008; Schmidt and Mandel, 2010).

Transfusion Recommendations

- Platelets can be given after resuscitation:
 - If the platelet count is $<5000/\text{mm}^3$ or
 - If there is a risk of bleeding or
 - If surgery or invasive procedures are planned (Dellinger et al., 2008)

Blood Pressure

The resuscitation goal is a mean arterial pressure ≥ 65 mm Hg. In about one-third of septic patients with hypotension, the blood pressure will rise sufficiently after intravenous fluids have been given. If adequate fluid administration does not improve the low tissue perfusion, then it is likely that the patient is in shock and vasopressors are needed. Dopamine and/or norepinephrine are the recommended first-line vasopressors. Vasopressors are typically given through a central venous catheter (Shapiro et al., 2010).

Mean Arterial Pressure (MAP)

Mean arterial pressure reflects a patient's overall tissue perfusion pressure, and it is frequently monitored when treating sepsis. The normal range of MAP is 70–110 mm Hg. Ischemia is likely if MAP is ≤ 60 mm Hg.

For patients in shock, blood pressure cuffs do not always give accurate blood pressure measurements. When vasopressors are being given, it is best to measure blood pressures with an indwelling arterial cannula (Dellinger et al., 2008; Morrell et al., 2009).

Cardiac Output

If the venous oxygenation saturation remains low and if it appears that cardiac output is reduced, consider using dobutamine (an inotrope) to increase the cardiac output. If it is not clear whether the cardiac output is below normal, a vasopressor (norepinephrine or dopamine) is typically combined with the dobutamine (Dellinger et al., 2008; Schmidt and Mandel, 2010).

It is recommended that cardiac output not be pushed above normal levels.

Septic Shock

Septic shock can be recognized by its refractory hypotension: specifically, aggressive fluid resuscitation will not adequately raise the patient's blood pressure.

Significant lactic acidosis—i.e., lactate levels >4 mmol/l—should be treated with the same high priority as refractory hypotension.

An experienced clinician should be able to recognize and to make an initial assessment of shock in a few minutes. For shock, resuscitation should start immediately and not be delayed by the collection of culture samples. Likewise, delays in admitting a patient to the ICU should not slow the initiation of the patient's resuscitation (Dellinger et al., 2008; Gaieski, 2010).

The resuscitation of patients in septic shock should continue until all target values are met—not just the blood pressure target.

Step 2: Begin Searching for the Infection

Targets During the Initial Search for an Infection

- Two or more blood culture samples:
 - One percutaneous
 - One from each vascular access device that has been in place >48 hrs
- Culture samples from other potentially infected sites (Dellinger et al., 2008)

Recommendations

Identify the Microbes

Beginning antibiotic therapy is a high priority: delays increase the risk of mortality. However, if it is possible, culture samples should be taken before starting the antibiotics; by identifying the causative microbe, treatment can eventually be switched to the most effective drug (Morrell et al., 2009).

Brief Search for the Source

A quick wide-ranging physical exam is the best way to begin the search for an infection. Surgical sites should be tested for warmth, redness, swelling, induration, or tenderness. Lungs should be auscultated, the abdomen palpated, the mouth, throat, nose, and ears looked at, and the head and extremities examined and palpated.

Any potential sites of infection should be cultured. If necessary, urine, cerebrospinal fluid, or respiratory secretions should also be cultured. All samples should be immediately transported to a microbiology lab (Dellinger et al., 2008).

Step 3: Give Empiric Antibiotics

Targets for the Initial Administration of Antibiotics

- Begin intravenous antibiotics quickly; if there is severe sepsis or septic shock, begin antibiotics within 1 hour
- Characteristics of an acceptable empiric antibiotic:
 - Broad-spectrum, covering all likely bacteria and fungi
 - Good tissue penetration into the probable site of the infection
- Use a combination of antibiotics for:
 - Pseudomonas
 - Neutropenic patients
- Reassess the antibiotic regimen daily (Dellinger et al., 2008)

Recommendations

Initial Drugs

As soon as all culture samples have been taken, patients should be started on an intravenous antibiotic regimen. Rapid administration of appropriate antibiotics has been shown to reduce mortality by 10%-15% in patients with severe sepsis, whereas a delay of only an hour is enough to raise mortality rates (Shapiro et al., 2010).

The choice of antibiotics should take into account the:

- Immune-competency of the patient
- Renal functioning of the patient
- Likely tissue of the primary infection
- Common pathogens of the hospital and the community
- Unless the causative microbe is known, the empiric antibiotics should be effective against gram-positive bacteria, gram-negative bacteria, and likely fungi.

A typical one-drug empiric antibiotic might be a third- or fourth-generation cephalosporin, carbapenem, or extended-spectrum carbapenem. A typical two-drug empiric regimen might be a beta-lactam combined with an aminoglycoside or a beta-lactamase inhibitor combined with ureidopenicillin. For a more detailed discussion of appropriate antimicrobial therapies and for tables of recommended antibiotic combinations, see (Munford, 2008), (Shapiro et al., 2010), or (Schmidt & Mandel, 2010).

Subsequent Drugs

Usually antibiotics are given for 7 to 10 days, although the detailed plan for any individual patients varies (Schmidt and Mandel, 2010). The patient's antibiotic regimen should be reassessed daily. If microbiology lab results identify the infecting microbe, the antibiotic regimen should be tailored for that organism and its particular drug susceptibilities.

In many cases of sepsis, microbiologic analyses can identify no infectious cause. For example, half of the cases of severe sepsis or septic shock will have negative blood cultures. In such cases, other evidence and clinical experience must be used to separate the patients with sepsis from the patients with noninfectious SIRS. If it is decided that the cause of a patient's septic-like syndrome is noninfectious, the antibiotics should be stopped (Dellinger et al., 2008).

Step 4: Search For and Treat Sites of Infection

Targets for a Thorough Search for and Control of the Underlying Infection

- Within the first 6 hours, physically and radiographically search for the site(s) of an infection
- Sample and culture any potential sites
- Formulate a plan for source control (eg, removing infected devices, draining abscesses, or debriding tissue)
- After fluid resuscitation, carry out the source control plan (Dellinger et al., 2008)

Recommendations

Even with appropriate antibiotics, many infections can only be fully controlled when the source is removed, drained, or cleaned. Sometimes, the infection is clinically obvious or it can be clearly inferred from the medical history. At other times, however, it is necessary to conduct a quick but thorough search. Here are some search suggestions.

Sites to Search

- **Catheters.** All indwelling cannulas, lines, and catheters are potential sources of the infection underlying sepsis. Wherever possible, remove indwelling tubes, roll each tip in a culture plate and, after antibiotic therapy is initiated, insert a replacement catheter in a new site. Replace Foley and other drainage catheters (Glickman et al., 2010).
- **Wounds.** Inspect surgical and traumatic wound sites by removing their dressings. Look for signs of infection, such as swelling, purulent discharge, erythema, increased warmth, tenderness, or crepitus. A plain film of suspicious areas can show gas from necrotizing tissues.
- **Lungs.** The respiratory system is the most common site of the infection causing an episode of sepsis. Ask a septic patient about chest pain, dyspnea, and productive cough. Be alert to tachypnea. Carefully auscultate the chests of ill patients who have a high respiratory rate, because tachypnea can be the first sign of a developing pneumonia (Shapiro et al., 2010).

- **Heart.** Fever with a heart murmur, a history of intravenous drug use, prosthetic heart valves, or mitral valve prolapse suggests the possibility of endocarditis. Look for skin signs of endocarditis, which will support the diagnosis. In patients with endocarditis, a transesophageal echocardiogram will sometimes show valve vegetations (Shapiro et al., 2010).
- **Abdomen.** Ask a septic patient about abdominal pain, nausea, vomiting, and diarrhea. Then, look for signs of cholecystitis, appendicitis, or diverticulitis. In your search, remember that noninfectious acute pancreatitis can trigger SIRS (Jui, 2010). A plain film of the abdomen is useful because it can show a paralytic ileus, signs of stomach or bowel perforation, or an abscess. An abdominal ultrasound can reveal a number of gallbladder and biliary tree problems, as well as fluid pockets and abscesses. An uncertain diagnosis can often be confirmed by a CT scan.
- **Genitourinary tract.** Ask a septic patient about flank or pelvic pain, dysuria, and genital or urinary discharge. Consider acute pyelonephritis. Find out whether there is a recent history of genitourinary procedures and, in women, whether there has been a recent pregnancy, birth, or abortion (Jui, 2010). Check for anogenital lesions and rectal tenderness; in women, also check for adnexal tenderness and for evidence of cervical or uterine infection. Ultrasound or CT can be used to search for pelvic abscesses.
- **Head.** Look for evidence of sinusitis: orbital pain, tender sinuses, or edema. Ask whether the patient has had any recent nasotracheal or nasogastric intubations. Check for ear, pharyngeal, or tonsillar infections. An uncertain diagnosis can often be confirmed using a CT scan.
- **Central nervous system.** Meningitis can trigger sepsis. Ask a septic patient about headache, vomiting, stiff neck, and photophobia, and look for nuchal rigidity, fever, altered mental state, papilledema, or petechial skin rashes. Consider obtaining a sample of cerebrospinal fluid.
- **Skin.** Look for ulcers or cellulitis. Also, look for lesions, petechiae, or rashes that may be clues to the underlying infection; such skin signs are sometimes seen, for example, in *Neisseria meningitidis* infections, staphylococcal toxic shock syndrome, and endocarditis (Jui, 2010).
- **Blood.** When the physical examination cannot find a source for severe sepsis or septic shock, consider the possibility of a primary bacteremia or endocarditis (Jui, 2010).

Source Control

Source control means removal of the nidus of the infection and of any necrotic tissue. Abscesses must be opened and drained. (Deep abscesses can be drained by catheter.) Infected tissue should be debrided, sections of infected hollow organs should be excised, and foreign bodies that are colonized by microbes should be removed. Some infections, such as clostridial myositis may require limb amputation.

Step 5: Sepsis-Specific Medications

By the end of the initial six hours, a septic patient should be stable and on antibiotics, and any accessible sources of infection should have been cleaned or removed. With the completion of these treatment steps, the patient's chances of survival have been improved and further management becomes mainly supportive care of a critically ill patient.

As a patient with sepsis, however, an increased chance of mortality continues. Scientists have worked with minimal success to find drugs that will reduce the sepsis-specific risks of dying. According to Lee and Slutsky (2010):

Despite intensive research over decades, few new therapies have been developed, and the mainstay of treatment remains nonspecific supportive care. Indeed, sepsis has been described as the “graveyard” of pharmaceutical discovery because most drugs that appeared promising based on in vitro and animal models have proved to be ineffective in humans.

A recent disappointment, for example, is drotrecogin alfa (Xigris), which is human recombinant activated protein C (rhAPC). An earlier study had suggested that this drug might increase survival rates of high-risk patients with severe sepsis (Jui, 2010; Schmidt and Mandel, 2010). Recent studies, however, failed to confirm the drug's benefits and it has been withdrawn from the market.

Corticosteroids

The concept that sepsis is an out-of-control inflammatory response has long suggested that anti-inflammatory drugs may help septic patients to recover. However, clinical trials of corticosteroids have given inconclusive results, and the use of corticosteroids for sepsis is controversial.

The latest guidelines from the Surviving Sepsis Campaign (Dellinger et al., 2008) recommend that using intravenous hydrocortisone (200–300 mg/day) in septic shock when the patient's hypotension is not adequately reversed by fluid resuscitation and vasopressors. One risk of corticosteroid therapy is that an immunosuppressed septic patient can develop additional infections. The use of corticosteroids in septic shock is still being actively debated (Morrell et al., 2009; Shapiro et al., 2010).

Continued Management of Sepsis

At this point in the management of a septic patient, care becomes supportive, with special attention to solving individual problems as they arise. **Septic patients should be monitored continuously.**

A central venous catheter will usually be in place when supportive care begins. The catheter continues to be used for infusing fluids, medications, and blood products; it can be a source for blood samples; and it can be used to measure central venous pressure and central venous O₂ saturation, indicators of the patient's overall level of tissue perfusion.

Although arterial blood gases give the most direct information about the patient's gas exchange, in most cases ICUs take arterial readings intermittently and rely instead on pulse oximetry for minute-to-minute feedback.

Once a staple of critical care monitoring, pulmonary artery catheters (Swan-Ganz catheters) are now being used more selectively (Weinhouse, 2010). Some clinicians recommend against the routine use of pulmonary artery catheters for sepsis, severe sepsis, or septic shock (Schmidt and Mandel, 2010).

Specific Organs

The lungs and the kidneys often function poorly in sepsis and require special attention during the supportive care phase of management.

The Lungs and Mechanical Ventilation

Patients with sepsis should be given supplemental oxygen and monitored continuously using pulse oximetry. The treatment goal is to maintain $\text{SaO}_2 \geq 88\%$ (Ely and Goyette, 2005).

In severe sepsis, patients will likely require mechanical ventilation at some point during their hospitalization. Mechanical ventilation reduces the work of the respiratory muscles and can reduce the body's production of lactic acid. In addition, when patients are being ventilated mechanically, their respiratory muscles need less blood flow, freeing more of the cardiac output for other hypoperfused tissues.

Mechanical ventilation increases intra-airway pressures by actively pushing air into the lungs. Inflating the lungs using internal pressure increases the overall intrathoracic pressure; in turn, the increased intrathoracic pressure can compress the heart and great vessels and lower the mean arterial pressure, especially in conjunction with the relaxant drugs used to maintain intubation. The hypotension that sometimes occurs with positive pressure mechanical ventilation is more common when the patient is hypovolemic, so additional fluids may improve the blood pressure levels (Kress and Hall, 2008).

Clinical Indicators of the Need for Mechanical Ventilation

- Central venous oxygen saturation cannot be maintained $>70\%$
- Severe acidosis
- Reduced level of consciousness, making patients unable to protect their airways
- Work of breathing becomes exhausting. Clinically, fatigue of the respiratory muscles is likely when the rate of respiration is high (>40 breaths/min), the patient is unable to complete a full sentence without taking additional breaths, or the patient is using accessory muscles of respiration
- ARDS has developed (see ARDS box, above) (Ely and Goyette, 2005)

To minimize lung injury, patients are usually ventilated using positive end expiratory pressure at low tidal volumes (6 ml/kg body wt) and low plateau pressures ≤ 30 cm H_2O . Elevating the head of the patient's bed helps to prevent ventilator pneumonias (Dellinger et al., 2008; Morrell et al., 2009).

Extubation

To recognize when patients can be taken off mechanical ventilation, they should be given daily trials of spontaneous breathing. A trial begins with a check for the necessary baseline conditions:

- Sufficient oxygen exchange, as indicated by $\text{PaO}_2/\text{FIO}_2 > 200$ at a low positive end expiratory pressure (ie, $< 5 \text{ cm H}_2\text{O}$)
- No vasopressors or sedatives being given
- Cough and other airway reflexes working

If these conditions are met, the patient is asked to breathe through the endotracheal tube for 30 to 120 minutes without the aid of the ventilator.

A trial is stopped and the ventilator is reattached if the patient's:

- Respiratory rate increases to > 35 breaths/min for > 5 min **or**
- Oxygenation saturation drops below 90% or
- Heart rate increases to > 140 beats/min or the heart rate increases or decreases $> 20\%$ from its baseline
- Systolic blood pressure drops to < 90 mm Hg or rises to > 180 mm Hg
- The patient's anxiety level or sweating increases

A patient who has none of these problems during the test period and who ends with a respiratory rate-to-tidal volume ratio of < 105 can then be extubated.

Source: Kress and Hall, 2008.

Kidneys

Temporary periods of low urinary output are common in severe sepsis and septic shock, but anuria or acute renal failure is less frequent. Nonetheless, when kidney failure does occur it increases the chance of mortality.

There are currently no drugs that can protect the kidney during an episode of sepsis. The best the clinician can do is to avoid hastening the damage. When under-perfused, the kidneys are especially vulnerable to injury from drugs, so physicians should avoid administering any medicines that are kidney stressors or are potentially nephrotoxic. According to Ely and Goyette,

For example, nonsteroidal anti-inflammatory drugs used to treat fever can inhibit the production of prostaglandins by the afferent arterioles and impair the ability of the kidney to regulate its blood flow. In the patient with severe sepsis and decreased blood volume, this may be enough to precipitate acute tubular necrosis. (2005)

Therefore, when a required drug is potentially nephrotoxic (eg, the aminoglycosides), it should be given in doses adjusted for the patient's level of kidney function.

If it appears that acute kidney failure is beginning (lab results show high BUN, high serum creatinine, hyperkalemia, acidosis, or volume overload) either intermittent hemodialysis or continuous renal replacement therapy can be instituted for most patients. Patients who are hemodynamically unstable, though, do better on continuous renal replacement therapy (Dellinger et al., 2008). It can take weeks for survivors of sepsis to regain their normal kidney function.

Body Temperature

Sepsis often produces an abnormal body temperature—either fever ($>38^{\circ}\text{C}$) or hypothermia ($<36^{\circ}\text{C}$). Typically, the body corrects its temperature after the septic infection has been controlled.

Fever

Usually, mild fever in a septic patient can simply be monitored, but higher temperatures ($>40^{\circ}\text{C}$) should be treated, especially in patients with pre-existing heart, lung, or brain disease. Feverish patients can be given antipyretics (eg, acetaminophen). Alternately, cooling blankets or tepid water sponging can be used. Fever increases the body's consumption of energy and oxygen, and this will worsen the effects of poor tissue perfusion from sepsis.

Hypothermia and Shivering

Mild hypothermia usually improves with a blanket. Shivering increases the patient's energy and oxygen use, and persistent shivering is often treated with meperidine.

Nutrition

Daily Requirements

A patient with sepsis will be in the ICU for 1 to 2 weeks. Proper nutrition can shorten the stay. A patient's basal caloric and protein needs are calculated from their body weight (the average daily energy baseline is 25–30 kcal/kg). Sepsis puts the body in an energy-using, catabolic mode, so a patient with sepsis is typically given 50% to 100% more calories than their baseline requirement.

In general, glucose should supply 30% to 70% of a critical-care patient's nonprotein calories, and lipids should supply 15% to 30% of the nonprotein calories. The lipid nutrients should include omega-3 fatty acids. Glutamine and arginine supplements are also recommended.

Feeding via the gastrointestinal tract is preferred. "Enteral nutrition offers several advantages, including lower cost, preservation of the GI mucosal barrier, buffering of gastric acid, preservation of enteral hormone secretion, provision of unique nutrients, decreased incidence of infections, improved wound healing, and avoidance of parenteral nutritional catheters and their complications" (Ely & Goyette, 2005). For patients receiving enteral feedings, the head of the bed should be elevated 30° to 40° (Morrell et al., 2009).

Hyperglycemia

Hyperglycemia is induced by stress, and it is common in critically ill patients, even patients who have no history of diabetes (Schmidt and Mandel, 2010). Hyperglycemia worsens sepsis by many routes. Hyperglycemia promotes inflammation, it hinders normal immune functioning, and it activates the extrinsic blood coagulation pathway. Consistently high levels of blood glucose also alter the body's fluid balance and directly damage the kidneys and the peripheral nerves, among other tissues (Munford, 2008).

It is recommended that blood glucose levels be kept <150 mg/dl for septic patients and that intravenous insulin should be the drug used to control episodes of hyperglycemia. Patients on intravenous insulin need a scheduled source of glucose calories, and their blood glucose levels must be monitored regularly (every 1–2 hours at first, and every 4 hours when the blood values are stable) (Dellinger et al., 2008).

Protective Measures

As with all those in an ICU, patients with sepsis are at risk for additional complications, including the development of deep venous thromboses, gastrointestinal bleeding, and skin lesions (Morrell et al., 2009). The supportive care of septic patients should include protective measures against these and all other ICU-fostered complications.

Deep-Vein Thromboses

Immobile patients are at risk for developing thrombi in the deep veins of their lower (or, less frequently, upper) limbs with the potential for emboli to the lungs and elsewhere. This risk increases in a septic patient, who is likely to be elderly and to have a central venous access device in place. Moreover, in patients with severe sepsis, the tendencies of the coagulation system are usually weighted toward clotting rather than fibrinolysis.

The recommended deep-vein thrombosis prophylaxis for patients with sepsis begins with heparin. If heparinization is contraindicated, such as when the patient has active bleeding, low platelet counts, or a recent intracerebral hemorrhage, compression stockings or other compression devices are recommended (Dellinger et al., 2008).

Stress Ulcers

Patients with severe sepsis are at risk for developing upper GI bleeds. This risk is greatest in a patient who is on mechanical ventilation, who has a coagulopathy, or who has a history of peptic ulcer disease. Therefore, an H₂-blocker (eg, ranitidine) or a proton pump inhibitor (eg, omeprazole) should be considered as part of the care routine for sepsis. A qualifier to this recommendation is that a decrease in stomach acid production will increase the risk of pneumonia in a ventilated patient (Dellinger et al., 2008).

Balancing Life Support and End-of-Life Decisions

Vincent and colleagues assert:

Death in the ICU is now often preceded by a decision to withhold or withdraw potentially life-sustaining treatments. . . [One recent analysis found that] potentially life-sustaining treatments were withheld or withdrawn before death [for 91% of the patients who eventually died]. Approximately two-thirds of these patients had treatments withdrawn because death was imminent and one-third because the treatments were judged to be inappropriate. (2011)

The technical support of a gravely ill patient in an ICU can dominate the patient's last days and nights and leave little room for the human interactions that many patients and their families want. It is important for ICU doctors and nurses to talk with their patients and the patients' families about the "appropriate application and withdrawal of life-sustaining therapies" (Dellinger et al., 2008). Giving realistic information early and allowing patients and families to talk about their wishes can reduce the levels of anxiety and depression that the circumstances inevitably produce (Dellinger et al., 2008).

Prognoses for Patients with Sepsis

Mortality During the Current Hospitalization

When sepsis becomes severe, it has a high mortality rate. Even with appropriate care, 20% to 35% of patients with severe sepsis will die within thirty days. As the severity increases, so does the risk of mortality. For example, if septic shock develops, 35% to 60% of patients will die within 30 days, and the survivors will face an increased risk of mortality for at least five years afterward (Munford, 2008).

Clinicians have learned that early identification of those septic patients with the highest risk of dying allows interventions that can lower the mortality rates. This has driven research on ways to measure the severity of a patient's sepsis and to recognize patients with the poorest prognoses.

APACHE-II, the revised Acute Physiology and Chronic Health Evaluation

The Apache-II score assigns a severity level to a patient's illness, using data that are straightforward and commonly available. The APACHE-II scoring form comprises:

- Two questions about medical history ("Does the patient have a history of chronic organ insufficiency or immuno-compromise?" "Does the patient have acute renal failure?")
- The patient's age
- Four vital signs (temperature, heart rate, respiratory rate, mean arterial pressure)
- Three basic serum concentrations (sodium, potassium, creatinine)
- Four blood values (hematocrit, white blood cell count, arterial pH, arterial oxygen concentration)
- One mental status measure (Glasgow coma score) (Knaus et al., 1985)

APACHE-II scores range from 0 to 71, with higher scores indicating more severe illnesses and poorer prognoses.

APACHE is one of a number of objective rating systems currently in use. These measures are helpful in characterizing populations (groups of patients) in clinical studies; they are less helpful in making predictions about individual patients (Liu and Gropper, 2009).

Scoring Systems

Critical care physicians have developed a number of ranking systems for comparing the severity of illness of ICU patients. The most widely used system is the APACHE classification (Knaus et al., 1985). (See APACHE box, above.) Other important rating systems include the:

- Mortality Probability Model (Vasilevskis et al., 2009)
- Second Simplified Acute Physiology Score (Le Gall et al., 1993)
- Sequential Organ Failure Assessment (Vincent et al., 1996, 1998)
- Multiple Organ Dysfunction Score (Marshall et al., 1995)
- Logistic Organ Dysfunction System (Le Gall et al., 1996).

These rating systems are used as the standardized measurement tools in clinical trials, where the goals are to describe populations of patients. However, the rating systems have proven cumbersome and difficult to normalize in the daily care of individual septic patients (Martin & Wheeler, 2009; Tiruvoipati et al., 2010).

Kress and Hall state:

Severity-of-illness scoring systems suffer from the problem of inability to predict survival in individual patients. Accordingly, the use of these scoring systems to direct therapy and clinical decision-making cannot be recommended at present. Rather, these tools should be used as important data to complement clinical bedside decision-making. (2008)

Counting Organ Failures

Septic patients with failing organs are at increased risk for dying, and the risk increases as the number of organ failures increases. In fact, the main cause of death in patients with severe sepsis is multiple organ failure (Vincent et al., 2011).

One of the most reliable predictors of the likelihood of mortality for patients is the number of their organs or organ systems that are malfunctioning. A simple count of the number of organ failures provides a general prognosis. For example, in one study of critically ill patients, these death rates were found:

Likelihood of Death Increases in Sepsis with Number of Failing Organs	
Number of dysfunctional organs	Death rate
0	9%
1	22%
2	38%
3	69%
4 or more	83%

Source: Vincent et al., 2011.

Counting Predictive Risk Factors

In addition to the number of failing organs, many other factors have been found to identify septic patients with higher than average mortality rates. By counting a patient's number of predictive risk factors, we can rank the patient's chance of dying, because more risk factors indicate a higher risk of mortality (Munford, 2008).

The following list enumerates many of the currently identified predictive risk factors for mortality in patients with sepsis.

Predictive Risk Factors for Increased Mortality from Sepsis

- Patient's age
 - Older than 40 years
- Patient's medical history
 - Has a concurrent disease (eg, AIDS, alcoholism, cirrhosis, cancer, liver failure, renal failure)
 - Is immunosuppressed
 - Is malnourished
 - Admitted to ICU from an inpatient floor instead of through ED
- Blood pressure
 - Persistence of hypotension (systolic BP <90 mm Hg)

- Body temperature
 - Persistently low temperature ($<35.5^{\circ}\text{C}$)
 - Persistently high temperature ($>40^{\circ}\text{C}$)
- Cardiac
 - Persistence of tachycardia (>124 beats/min)
- Pulmonary
 - Persistence of tachypnea (>29 breaths/min)
- Neurologic
 - Develops septic encephalopathy
 - Glasgow Coma Score <13
- Site of primary infection
 - Pulmonary
 - Gastrointestinal
 - Undetermined
- Microbe(s) causing primary infection
 - Staphylococcus aureus
 - Pseudomonas
 - Non-Candida fungus
 - Polymicrobial
 - Nosocomial (hospital-acquired) infection
- Blood cells
 - Leukopenia (white blood cell count <4000 cells/mm³)
- Blood chemistry
 - Elevated venous lactate level (normal = 0.4–2.2 mmol/l)
 - Reduced blood concentration of activated protein C early in the sepsis (Martin and Wheeler, 2009; Nevieri, 2010a,b; Tiruvoipati et al., 2010)

Proactive Steps

Prevention

In the United States, severe sepsis and septic shock usually develop from nosocomial infections (infections acquired in the hospital) (Mody, 2007). There is now a medical specialty, infection prevention, charged with reducing healthcare-acquired diseases, and infection preventionists are on staff in many medical institutions to organize and oversee infection control programs (Cook et al., 2011).

Control programs prescribe infection precautions and ensure that they are strictly followed. Preventionists set up handwashing campaigns. They advocate for the aggressive treatment of nosocomial infections and for the isolation of patients with drug-resistant infections. In some hospitals, preventionists are running trials of disease-resistant devices, such as antibiotic-coated vascular catheters (Kress and Hall, 2008).

Preventionists also work to modify medical habits. Examples of a typical preventionist's agenda for their colleagues include:

- Encouraging reductions in the number of invasive procedures performed
- Encouraging reductions in the use and duration of indwelling catheters (vascular and urinary)
- Discouraging the unnecessary use of antimicrobial drugs
- Encouraging limitations on the length of time during which a broad-spectrum empiric antibiotic is administered
- Encouraging glucocorticoids to be given purposefully and not simply reflexively (Mody, 2007; Owens, 2009)

Treatment Optimization

Patients with sepsis fare best in medical centers experienced in managing the condition. Hospitals that have instituted an organized plan for recognizing and treating sepsis have shorter ICU stays and lower mortality rates for patients with sepsis. The Surviving Sepsis Campaign has assumed the task of helping hospitals to improve their sepsis care. The campaign publishes evidence-based guidelines for managing sepsis. It also distributes instructions for setting up effective treatment facilities and for educating healthcare workers in the recommended procedures (website at <http://www.survivingsepsis.org/Pages/default.aspx>) (Levy, et al., 2010).

The Methodist Hospital in Houston, Texas (McKinley et al., 2011) is a role model for hospitals planning to apply the campaign's sepsis management program. The Methodist Hospital has used the Surviving Sepsis Campaign's guidelines to develop software that keeps records and that offers recommendations for the triage and the treatment of sepsis in their surgical ICU. The computerized system has been set up so that it is regularly re-examined and retuned, and the program continues to improve.

The Hospital's software compiles comprehensive flow sheets and current patient summaries. It provides lists of care suggestions, including continually updated recommendations of time-sensitive interventions. It identifies points at which an experienced intensive care specialist should be consulted. It also offers a baseline against which doctors and nurses can check their clinical reasoning.

The hospital's self-evaluations show that even those staff members who rotate in and out of the ICU can use the computerized system effectively. As a result of implementing the program and the software, the surgical ICU's mortality rate for severe sepsis and septic shock dropped from 34% to 14% in three years (McKinley et al., 2011).

Summary

Sepsis is a potentially lethal syndrome that is usually managed in an ICU. When the septic response is triggered by an infection, inflammation can be found throughout the entire vascular tree of the body. Inflammatory molecules pour into the circulation and spread through the body, injuring the endothelium that lines the blood vessels. The damaged vascular endothelial cells reduce perfusion into adjacent tissues, and organs or portions of organs become hypoxic.

Capillaries with injured endothelia become leaky, and in sepsis, blood volume is lost. Under the many-pronged onslaught of systemic inflammation and organ dysfunction, the normal systemic mechanisms can no longer replenish the depleted blood volume. The result is hypovolemia and a further reduction in the perfusion of tissues. Without treatment and supportive medical management, hypoxia causes key organs to fail, and, as more organs begin to fail, the patient becomes more likely to die.

In sepsis, volume loss is a critical problem. To resuscitate a septic patient, liters of fluid must be administered. Sometimes, however, even copious fluid resuscitation cannot shore up the patient's dropping blood pressure; at this point, septic shock has set in. Even with optimal treatment, mortality from severe sepsis or septic shock averages 40% percent and can exceed 50% in the sickest patients.

In its early stages, sepsis can resemble a variety of other disorders, so it can be difficult to diagnose. Rapid diagnosis, however, is essential because sepsis is a worsening disorder with a mortality rate that steadily increases the longer treatment is delayed.

Clinical studies have led to a widely applicable protocol optimizing the diagnosis and treatment of sepsis. The protocol, built on achieving specific physiologic targets, lays out four consecutive treatment steps: fluid resuscitation, collection of data and initial search for the infection, administration of antibiotics, and control of the infection. It is recommended that these steps be completed in less than 6 hours, after which time supportive critical care should be instituted.

Briefly, the protocol for the first 6 hours is:

- Step 1. Treatment, which should begin as soon as the patient presents, begins by ensuring a patent airway. The patient should then be resuscitated with intravenous fluids. An early target is to raise the central venous oxygen saturation to 70% or higher. To reach this and the other hemodynamic targets (central venous pressure = 8–12 mm Hg, mean arterial pressure >65 mm Hg, urine output >0.5 ml/kg/h, and hematocrit >30%), vasopressors, inotropes, or red blood cell transfusions may be needed.
- Step 2. Basic diagnostic data should be collected and a brief search for the site of the infection needs to be made. The initial data should include blood work and blood cultures; all possible sites of infection should also be cultured.
- Step 3. The underlying infection must be treated, because sepsis is difficult to stop unless the infection is controlled. When the microbe causing the infection is unknown, broad-spectrum antibiotics are started. Giving antibiotics should not be delayed by long searches for the infection. In one large study of septic shock, 80% of the patients survived if given an appropriate antibiotic within 1 hour, but each additional hour of delay reduced the survival rate by 8%.
- Step 4. Any infected or potentially infected sites should be drained, cleaned, or removed, because persisting pockets of microbes will continue to trigger the septic reaction. All indwelling devices are examined and, if infected, must be removed. Surgical advice or participation is often needed because abscesses and empyemas must be drained and infected tissues should be debrided or resected.

Finally, protective and supportive measures for a critically ill patient are set in place. These provisions include ensuring adequate nutrition, treating hyperglycemia, and instituting prophylaxis against deep venous thromboses and stress ulcers.

Sepsis is common: in 2011, there will be more than 900,000 cases of sepsis in the United States, and the number of cases is projected to continue increasing each year thereafter. Sepsis is also expensive: the average medical cost is >\$22,000 per case.

Sepsis is a major concern of the critical care health system. More than half of the patients with severe sepsis need ICU care. And, although 2% to 3% of all hospitalized patients have severe sepsis, those patients account for 20% of hospital ICU admissions.

In spite of intensive research, sepsis remains potentially fatal. Severe sepsis and septic shock are the tenth leading cause of death in the United States, officially accounting for 9.3% of all deaths each year. This statistic is probably too low. Organ failure is more often listed as the cause of death than is the sepsis that caused it, and it has been estimated that sepsis actually causes or contributes to approximately 30% of all U.S. deaths.

Together, the European Society of Intensive Care Medicine, the International Sepsis Forum, and the Society of Critical Care Medicine have organized the Surviving Sepsis Campaign. This program is an international effort to define and publicize a plan for effectively managing sepsis and minimizing mortality. The program sponsors studies, compiles databases, and publishes detailed peer-reviewed guidelines for the care of patients with all forms of sepsis. Full information is available on their website at <http://www.survivingsepsis.org/Pages/default.aspx>.

Resources

Basic Information

These government websites are accurate and clearly organized. They include information for the public and references to more detailed sources for professionals.

- <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001687/>
- http://www.nigms.nih.gov/Education/factsheet_sepsis.htm
- <http://www.nlm.nih.gov/medlineplus/sepsis.html>

Detailed Information

For professionals, the website of the International Surviving Sepsis Campaign is a good source of information and references.

- <http://www.survivingsepsis.org/Pages/default.aspx>

Treatment Guidelines

Comprehensive treatment recommendations were published in a 2008 article entitled "Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008." A citation to this article is under "Dellinger, RP, et al. (2008)" in the References listed below. The article is also available on the Internet at

- <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2249616/?tool=pubmed>

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(Post test begins on next page)

Post Test

Use the Answer Sheet following the test to record your answers. There are 28 questions.

1. The increase in the number of sepsis cases is, in part, due to:
 - a. Recent changes in the definition of sepsis.
 - b. More Americans visiting foreign countries.
 - c. Increasing longevity of people with immune-compromising diseases.
 - d. Increases in teen pregnancies.
2. Sepsis tends to strike:
 - a. Unsuspecting healthy young adults.
 - b. The ill and elderly people.
 - c. Teens.
 - d. Pet owners.
3. Which is correct regarding the relationship between sepsis and SIRS (systemic inflammatory response syndrome)?
 - a. Sepsis can lead to shock, while SIRS never produces shock.
 - b. SIRS is a type of sepsis that is caused by an infection.
 - c. SIRS can lead to shock, while sepsis never produces shock.
 - d. Sepsis is a type of SIRS that is caused by an infection.
4. Commensal ("normal flora") bacteria:
 - a. Rarely cause sepsis.
 - b. Commonly cause sepsis.
 - c. Rarely infect immunosuppressed patients.
 - d. Are, in general, medically harmless.
5. Cytokines are:
 - a. Signaling molecules used by the immune system.
 - b. Produced by bacteria and often toxic to humans.
 - c. A class of antibiotics used to treat sepsis.
 - d. Immune cells attracted to infected tissue.
6. A characteristic of sepsis that is fostered by increased concentrations of bradykinin, histamine, and prostaglandins is:
 - a. Itchy skin.
 - b. Occasional hypothermia.
 - c. Metabolic acidosis.
 - d. Leaky capillaries.
7. Compared to a typical inflammatory reaction, the inflammation in sepsis:
 - a. does not cause a fever.
 - b. is not associated with a change in the white blood cell count.
 - c. is not automatically terminated.
 - d. does not typically raise the heart rate.

8. One of the key early steps in the destruction caused by all types of sepsis is damage to:
 - a. Skin epithelial cells.
 - b. Vascular endothelial cells.
 - c. Red blood cells.
 - d. Skeletal muscle cells.
9. Acute respiratory distress syndrome (ARDS) is:
 - a. Sudden-onset pulmonary edema due to heart failure.
 - b. Another name for septic shock.
 - c. Typically caused by nosocomial (hospital-acquired) pneumonia.
 - d. The form of lung failure typically seen in sepsis.
10. In sepsis, lactic acid levels are increased by:
 - a. An increase in anaerobic metabolism due to poor tissue perfusion.
 - b. A high respiratory rate that raises the blood concentration of CO₂.
 - c. The liver's change from anaerobic to aerobic metabolism.
 - d. Hyperglycemia.
11. Death from sepsis is most often the result of:
 - a. Kidney failure.
 - b. The failure of more than one organ.
 - c. Pneumonia.
 - d. Lactic acidemia.
12. The best diagnostic tool for identifying sepsis is:
 - a. The patient's mean arterial pressure (MAP).
 - b. Clinical experience.
 - c. The patient's C-reactive protein (CRP) blood level.
 - d. The patient's blood level of procalcitonin.
13. Fever is a classic sign of a systemic infection. In sepsis:
 - a. Patients invariably have a fever.
 - b. Older patients tend to have a fever, but most patients have a normal or near-normal temperature.
 - c. Patients often have a fever, although some septic patients can have normal temperatures or even hypothermia.
 - d. A fever is rare.
14. The cardiac output is the:
 - a. Summative ECG.
 - b. Volume of blood that the heart pumps per minute.
 - c. Heart rate plus the respiratory rate.
 - d. Average of the systolic and the diastolic blood pressures.
15. Sepsis is triggered by an infection. The white blood cell count of a septic patient is:
 - a. Usually normal, surprisingly.
 - b. Always high.
 - c. Always low.
 - d. Usually abnormal but it can be either high or low.

16. When it has been possible to identify the microbe causing a case of sepsis, the microbe is most often a:
- Virus.
 - Fungus.
 - Bacterium.
 - Protozoan.
17. Septic shock:
- Is caused by cardiac dysfunction, such as heart failure or a myocardial infarction.
 - Presents with hypotension that cannot be reversed by fluid resuscitation alone.
 - Typically presents with low blood lactate levels, low blood concentrations of CO₂, and polyuria.
 - Unlike noninfectious types of shock, requires immediate administration of antibiotics as the first priority of treatment.
18. Toxic shock syndrome is:
- Severe staphylococcal bacteremia but without shock.
 - Staphylococcal bacteremia that is typically diagnosed by positive blood cultures.
 - A form of septic shock triggered by bacterial toxins.
 - A rapid-onset sepsis causing severe lung injury, pulmonary edema, and hypoxemia and requiring mechanical ventilation.
19. Initial fluid resuscitation for sepsis:
- Attempts to improve tissue perfusion with copious intravenous colloids or crystalloids.
 - Provides sufficient electrolyte-rich fluid by mouth to counteract severe dehydration.
 - Should be delayed until 6 hours after the administration of antibiotics because it dilutes their concentration in the circulation.
 - Has been superseded by the early administration of corticosteroids.
20. Antibiotics are a key tool in treating sepsis. They should be given:
- As soon as sepsis is suspected and before any other treatment begins.
 - As soon as a patent airway and appropriate ventilation are ensured.
 - Along with intravenous fluids during the initial resuscitation.
 - As soon as basic patient data are collected and preferably right after blood cultures have been drawn.
21. Empiric antibiotics are:
- Also known as fourth-generation antibiotics.
 - Given before the microbes causing sepsis have been identified.
 - Coated antibiotic tablets to prevent irritation of the stomach.
 - Administered to SIRS patients as a prophylaxis.
22. Once a septic patient has been started on a particular empiric antibiotic regimen:
- It is critical to not change antibiotics and to give the full course of 7 to 10 days of treatment.
 - New antibiotics should be added if the patient's initial fever persists.
 - New antibiotics should be added if the patient's white blood cell count continues to rise.
 - The need for and the choice of antibiotic should be reassessed daily.

23. In sepsis, “source control” means:
- Reduction of nosocomial infections.
 - Guarding access to those Schedule II–controlled substances used for patients with sepsis.
 - Removal of the nidus of the infection and of any necrotic tissue.
 - Isolation of patients with sepsis.
24. Because sepsis is an out-of-control inflammatory reaction, corticosteroids:
- Have proved to be an ideal addition to the treatment of mild forms of sepsis.
 - Would seem to be helpful drugs, but they have not proved useful in most patients with sepsis.
 - Are currently used as drugs to prevent sepsis, especially in immune-compromised patients.
 - Are typically given as an adjunct or booster with empiric antibiotics.
25. During supportive care for sepsis, an indwelling central venous catheter cannot be used for:
- Measuring arterial systolic blood pressure.
 - Infusing fluids and medications.
 - Taking blood samples.
 - Measuring central venous blood pressure.
26. In septic patients, mechanical ventilation is:
- Only used as a last resort because of the difficulty of weaning patients from dependence on the machine.
 - Needed only when vasopressors are being used to treat hypotension.
 - Commonly needed.
 - Rarely needed.
27. Combating hyperglycemia by limiting blood glucose levels in septic patients to <150 mg/dl:
- Should be done using intravenous insulin.
 - Is critical for diabetic patients but not necessary for non-diabetics.
 - Will worsen survival rates and should be avoided.
 - Should be done by restricting glucose intake.
28. A count of the number of organ failures in a patient with sepsis identifies:
- The patient's current immune status.
 - Patients who will benefit from a transplant.
 - Those patients with an underlying gram-negative infection.
 - Patients who have a high risk of dying.

(Answer sheet follows on next page)

Answer Sheet

Sepsis

Name (Please print your name): _____

Date: _____

Passing score is 80%

- 1. _____
- 2. _____
- 3. _____
- 4. _____
- 5. _____
- 6. _____
- 7. _____
- 8. _____
- 9. _____
- 10. _____
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- 20. _____
- 21. _____
- 22. _____
- 23. _____
- 24. _____
- 25. _____

- 26. _____
- 27. _____
- 28. _____

(Course evaluation follows
on next page)

Course Evaluation

Please use this scale for your course evaluation. Items with asterisks (*) are required.

5 = Strongly agree

4 = Agree

3 = Neutral

2 = Disagree

1 = Strongly disagree

- *1. Upon completion of the course, I was able to:
- a. Define sepsis, severe sepsis, and septic shock.
 5 4 3 2 1
 - b. Identify the groups of people with the highest risk of developing sepsis.
 5 4 3 2 1
 - c. Summarize the major factors that coalesce to cause sepsis and list the key events in the systemic spread of a septic reaction.
 5 4 3 2 1
 - d. Name the important diagnostic signs and laboratory values suggestive of sepsis.
 5 4 3 2 1
 - e. Discuss shock and its identification in septic patients.
 5 4 3 2 1
 - f. Explain the four steps in the initial treatment of sepsis.
 5 4 3 2 1
 - g. Identify the effects on organs and organ systems as management of sepsis continues.
 5 4 3 2 1
 - h. Explain the scoring systems and other methods for determining a prognosis with sepsis.
 5 4 3 2 1
 - i. Discuss prevention and treatment optimization efforts as proactive approaches to sepsis.
 5 4 3 2 1
- *2. The course was written in a way that facilitated my learning.
 5 4 3 2 1
- *3. This course was free from commercial bias.
 5 4 3 2 1

- *4. The course met my continuing education needs.
 5 4 3 2 1
- *5. The material presented was supported by evidence.
 5 4 3 2 1
- *6. The author avoided the use of anecdotal information as the main source of material.
 5 4 3 2 1
- *7. The course was free of product promotion.
 Yes No**
- ** If you answered no, please answer #8.
8. Was product promotion the sole purpose of the presentation?
 Yes No**
- *9. It took me 60 minutes per contact hour to complete the course, test, and evaluation.
 Yes No**
- ** If your answer was no, how long did it take?

10. My professional educational level is (check one):

Nursing

- Nurse Aide LVN/LPN RN (diploma) RN (AD)
 BSN MSN Nurse Practitioner/Advanced Practice Nurse
 PhD/DNSc

Therapy

- OT Aide COTA OT MOT OTD
 PT Aide PTA PT MPT MSPT DPT PhD

Other (please specify): _____

11. I heard about ATrain Education from:

- Search engine Advertisement
 Government or Board website Returning customer
 Friend Publication (Magazine, etc.)
 Other _____

12. I found the ATrainCEU.com website easy to use:

- Yes No

13. Comments or suggestions (optional): _____

(Registration on next page)

Registration Information

Please answer all of the following questions (*required).

* Name: _____

* Address: _____

* City: _____ State: _____ Zip: _____

* Phone: _____

* Professional Designation: _____

* License Number and State: _____

Please email my certificate: Yes No

Email (required if you want your certificate sent by email): _____

(If you request an email certificate we will **not** send a copy of the certificate by US Mail.)

Payment Options

You may pay by credit card or by check.

Fill out this section only if you are **paying by credit card**.

3.5 contact hours: \$24

Credit card information:

Name _____

Address (if different from above): _____

City: _____ State: _____ Zip: _____

Card type: Visa MC American Express Discover

Card number _____ CVS # _____

Expiration date _____

Test Completion and Mailing Instructions

1. Complete all forms:

- Answer Sheet
- Evaluation Learning Activity
- Registration Form (this page)

2. If you are **paying by check**, prepare a check for \$24 made out to ATrain Education, Inc.

3. Mail the completed forms and your payment to:

ATrain Education, Inc
5171 Ridgewood Rd
Willits, CA 95490

When we receive your forms and payment, we will mail (or email, if you request it) your certificate of completion. If you have any questions or concerns, please call or contact us at Sharon@ATrainCEU.com. And thanks for taking the ATrain!