Sepsis: Immune Response Meltdown

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Contact hours: 5

Course price: $29

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Course Summary

This course provides you with a thorough examination of the epidemiology and pathophysiology of sepsis. It covers diagnosis of sepsis and septic shock. It describes treatment strategies, supportive therapy, and other treatment considerations. It also discusses key elements of the Surviving Sepsis Campaign.

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80% or higher on the post test, a completed evaluation form, and payment where required. No partial credit will be awarded.

Course Objectives

When you finish this course you will be able to:

1. Explain the pathophysiology of sepsis.
2. Define sepsis, severe sepsis, and septic shock.
3. Identify 3 groups of people with the highest risk of developing sepsis.
4. Summarize 3 important components of the body's response to infection during a sepsis episode.
5. Name 3 important diagnostic signs and laboratory values of sepsis.
6. Discuss the clinical presentation of septic shock.
7. Explain the three-hour and six-hour bundles in the treatment of sepsis.
8. Name 2 elements of supportive therapy in severe sepsis.
9. Identify 5 predictive risk factors for increased mortality from sepsis.
10.   Explain the scoring systems for determining a prognosis with sepsis.
11.   Discuss prevention approaches to sepsis.
12.   Explain the patient experience with sepsis and care measures.

Sepsis: The Immune System Nightmare

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 & Slutsky, 2010

Nancy Murphy, a 46-year-old female, who is in a confused state with a 3-day fever and a wet cough producing yellow bloody sputum, is taken to the emergency department by a friend. In the ED a chest x-ray reveals right lower lobe pneumonia. Vital signs are:

BP 122/68; T 100.1 F; R-22; P-88

The diagnosis is acute pneumococcal pneumonia. Though she is prescribed an antibiotic, because the ER is extremely busy it is overlooked.

After three hours of waiting for a bed she is admitted to the medical/surgical unit. It is two hours more before her antibiotic infusion is given and still no blood culture has been taken. Her responsiveness worsens and her vital signs continue to decline.

A rapid response team is called when her vital signs are:

BP 100/60; T 102.1 F; R-26; P-102; and an Sa02 of 86%

She is moved to ICU, when it is determined she has developed respiratory hypoxia and sepsis.

What is the possible cause for her sepsis and sudden decline? Is the delay in antibiotic administration a causative factor? Why should a blood culture be ordered before the initial antibiotic dose? Would you as the nurse know what to do to identify the cause and prevent further deterioration? What are the different stages of sepsis? What orders would you anticipate to treat sepsis? What can be done for Nancy while she is on your watch and care?

Sepsis is a life-threatening condition caused by an over-reactive immune response to an infection and is a major cause of death globally. Normally, when bacteria or other microbes enter the human body, the immune system efficiently destroys the invaders. In sepsis the immune system goes into overdrive, and the chemicals it releases into the blood to combat the infection trigger widespread inflammation that can ravage the entire body (Recknagel et al., 2012).

Most often, the infection is bacterial, but infections of fungi, viruses, and protozoa can also trigger sepsis. The infection can be bloodborne or 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** (have an abnormally low levels of white blood cells) are the most likely to develop a septic response to an infection. Because of our aging population and because medical care is increasing the longevity of immunocompromised patients, the cases of sepsis are increasing in the United States. Because there is difficulty identifying causes of death due to sepsis on death certificates the Centers for Disease Control and Prevention (CDC) estimate between 300 and 1000 deaths/100,000 are due to sepsis in the United States (Gaieski, 2013). It is significant that each year from 2004 to 2009 the incidence and prevalence of sepsis increased approximately 13% each year and a mortality rate of 35% to 50% was seen (Surviving Sepsis Campaign, 2011).

In a classic systemic infection, such as a strep throat, the body's immune response is self-limiting: the immune forces are called into action, the battle is fought, and the army retires. Sepsis begins like a typical infection and often it 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 fail. Instead of tapering off and disappearing, the inflammatory forces spread beyond the infected region.

The response begins as pro-inflammatory signal molecules enter the bloodstream in large numbers. As they travel through the vascular system, these molecules cause dilation and leaking of the endothelium that lines the blood vessels, causing damage. The usual orderly movement of oxygen, nutrients, and fluids through the capillary walls is disrupted and organs become hypoxic.

If the sepsis continues, organ hypoxia and damage becomes organ failure, and at this point the condition is called **severe sepsis**. Severe sepsis increases the likelihood that the patient will die. When the organ system that fails is the circulatory system, the arterial wall muscles can no longer contract sufficiently to maintain adequate blood pressure. Now the patient is in **septic shock,** and the chance of surviving declines further (Shapiro et al., 2010).

The systemic collapse that occurs in sepsis is called **systemic inflammatory response syndrome (SIRS)**. SIRS can be triggered by a variety of causes, including noninfectious causes 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 to remove or control the primary source of the infection.

Did You Know . . .

To optimize a patient's chance of survival, sepsis must be treated rapidly and efficiently. Every hour of delay in treatment reduces the average patient's survival by 8%.

Test Your Knowledge

The systemic collapse that occurs in sepsis is called:

- A. Disseminated intravascular coagulation (DIC).
- B. Systemic inflammatory response syndrome (SIRS).
- C. Acute respiratory distress system (ARDS).
- D. Acute inflammatory syndrome (AIS).   Answer: B
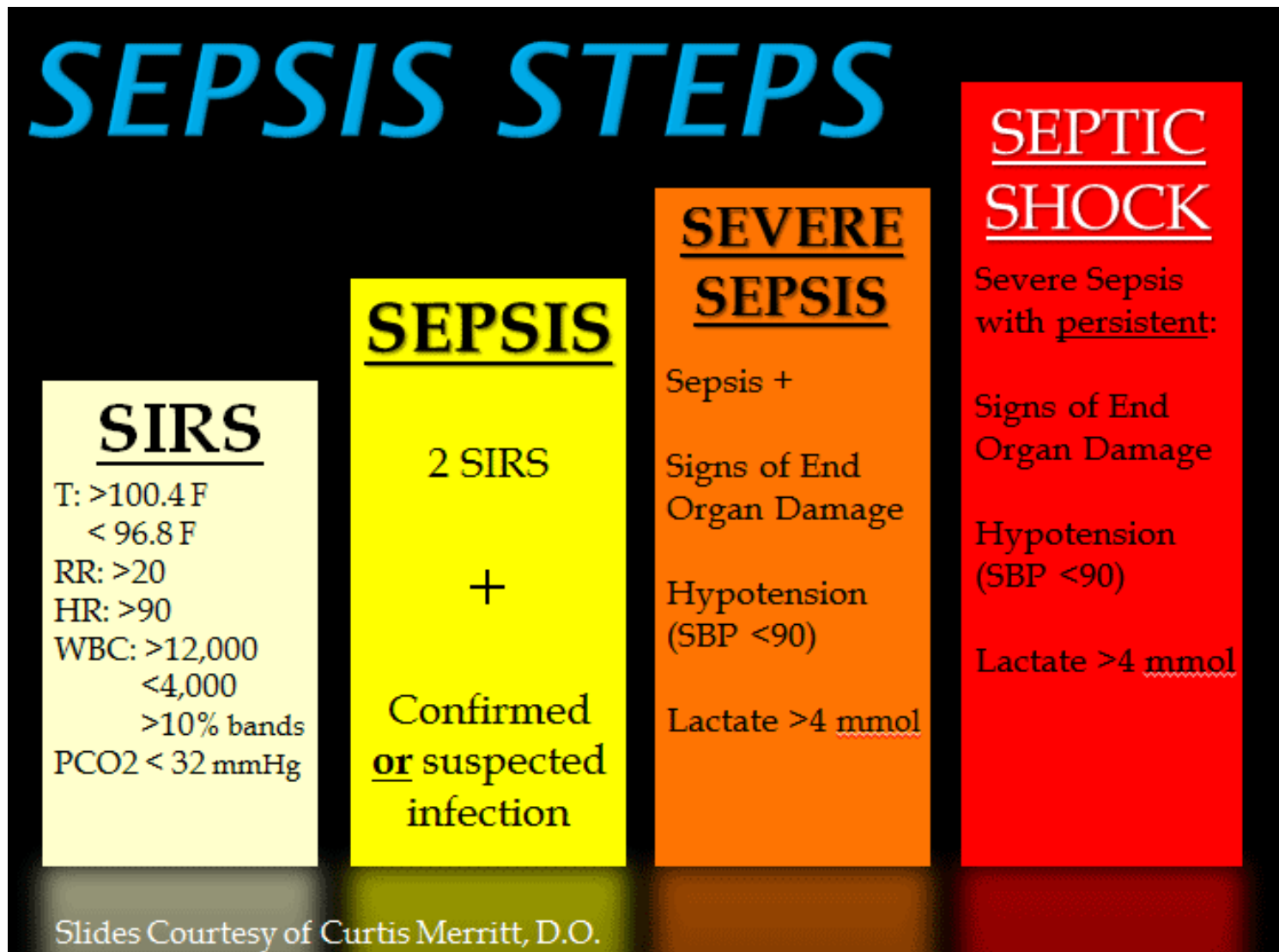
Apply Your Knowledge

The average patient who has sepsis 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. 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 (Daniels, 2011). More public attention was seen after sepsis claimed the life of celebrities Mohammad Ali and Patti Duke.

Clinical Definitions of Sepsis

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

Sepsis coexists with an infection, and often with other comorbidities, 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. Earlier terms for the syndrome included "blood poisoning," "bacteremia," and "septicemia," but in 1991 the American College of Chest Physicians standardized terminology to include, from mild to severe: infection, SIRS, sepsis, severe sepsis, septic shock, and multiple organ dysfunction syndrome (MODS).

SEPSIS STEPS

SIRS
T: >100.4 F
< 96.8 F
RR: >20
HR: >90
WBC: >12,000
<4,000
>10% bands
PCO2 < 32 mmHg

SEPSIS
2 SIRS
+
Confirmed or suspected infection

SEVERE SEPSIS
Sepsis +
Signs of End Organ Damage
Hypotension (SBP <90)
Lactate >4 mmol

SEPTIC SHOCK
Severe Sepsis with persistent:
Signs of End Organ Damage
Hypotension (SBP <90)
Lactate >4 mmol

Slides Courtesy of Curtis Merritt, D.O.

Source: Hadroncastle, Wikimedia Commons.

Infection is the presence of microorganisms causing an inflammatory response and triggering the natural immune system to fight the infection.

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

- Abnormal body temperature: hypothermia, <96.8°F/36°C; or fever, >100.4°F/38.3°C
- Tachycardia (>90 beats/min)
- Tachypnea (>20 breaths/min) or a rate sufficient to produce $PaCO_2$ <32 mm Hg)
- Abnormal white blood cell count (>12,000/mm^3, <4000/mm^3, or >10% immature WBCs)

SIRS is generally triggered by an infection that produces abnormal white blood cell counts, 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, 2013a,b). Untreated or unresolved SIRS can progress to sepsis, severe sepsis, septic shock, or MODS.

Sepsis is an uncontrolled complete-body response to an infection, regardless of whether the infection is local, extensive, or bloodborne. This over-reactive response *produces two or more of the signs of SIRS*. The septic reaction threatens to damage organs and to destabilize the circulatory system. Sepsis can lead to organ failure, shock, and death (Surviving Sepsis Campaign, 2011).

Severe sepsis, or *sepsis syndrome*, is present when the patient has progressed to a stage in which one or more organs or organ systems begin to fail. The Surviving Sepsis Campaign no longer uses the term *severe sepsis* but simply *sepsis*.

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 occurs when blood pressure cannot be maintained above 90 mmHg systolic despite adequate fluid resuscitation. The sepsis creates massive vasodilation and without adequate circulatory support and pressure, organs become hypoxic and can eventually die. Septic shock 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 failure and death. Septic shock is a form of distributive shock. In septic shock, there is hypotension and vasodilation that cannot be reversed by giving adequate fluids. When the hypotension of septic shock does not respond to vasopressors, the condition is called *refractory septic shock* (Munford & Suffredini, 2009).

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 or congestive heart failure.
- **Distributive**, in which sufficient fluid cannot be kept inside the vasculature, as in anaphylaxis, sepsis or neurogenic causes (Gaieski, 2013).
- **Multiple Organ Dysfunction Syndrome (MODS)** is 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.

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
- **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., 2013)
- **Mean arterial pressure (MAP)**—An indicator of general tissue perfusion-pressure, the arterial blood pressure is the driving force to push oxygen and nutrients from the vascular system into tissues and cells of the body. If cardiac output is constant, blood flow to tissues does not change until blood pressure falls below a critical value. Any additional decrease will compromise blood flow and oxygen to the organ. The

Surviving Sepsis Campaign (discussed later) recommends a MAP of >65 during the initial resuscitation period (Corrêa et al, 2013). Normal MAP is 70–110 mm Hg.

Test Your Knowledge

Severe sepsis, or sepsis syndrome, is:

    A.   The stage in which organs begin to fail.

    B.   Identified by the failure of three organs.

    C.   Sepsis that has progressed to suppurating wounds.

    D.   Seen when the patient is unconscious from admission to the ED.

Septic shock is:

    A.   Acute cardiac failure reversible with medication.

    B.   Preventable by adequate infection controls such as hand washing.

    C.   Acute circulatory failure with refractory hypotension.

    D.   Associated with pulmonary collapse.

Apply Your Knowledge

Q: In our case scenario, what kind of sepsis did Nancy Murphy have? Why?

A: She initially presented with a pneumonia that could be treated with antibiotics. Due to the delay in IV therapy, the inflammatory response moved in severity from an infection to SIRS and later to full sepsis.

Answers: A, C

Epidemiology of Sepsis

The Statistics

Severe sepsis is unfortunately 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 is more than the growth of the U.S. 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). It has been estimated that between 28% and 50% of these people die—far more than the number of U.S. deaths from prostate cancer, breast cancer, and AIDS combined (NIGMS, 2013).

The increasing number of sepsis cases in the United States may be due to:

- An aging population

- The increased longevity of people with chronic diseases

- Greater use of invasive procedures which introduce microorganisms into the body

- Broader use of immunosuppressive drugs, chemotherapy, and transplantation

- The spread of antibiotic-resistant organisms

- Improved clinical awareness and diagnosis of sepsis
  (NIGMS, 2013)

More than half of all patients diagnosed with severe sepsis are treated in an intensive care unit (ICU) and sepsis is one of the most common reasons for admission to ICUs throughout the world. 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).

During the past two decades, the incidence of sepsis in the United States has tripled and is now the tenth leading cause of death. In the United States alone, approximately 750,000 cases of sepsis occur each year and at least 225,000 (1/3) are fatal. Septic patients are generally hospitalized for extended periods, rarely leaving the ICU before 2 to 3 weeks. Despite the use of antimicrobial agents and advanced life support, the case fatality rate for patients with sepsis has remained between 20% and 30% during the past two decades (Marik, 2011).

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 costs 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 due to improvements in early diagnosis and effective treatments. 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. Overall, sepsis contributes to almost 30% of all U.S. deaths and almost 40% of the deaths of Americans older than 85 years (Munford, 2008; CDC, 2010).

Susceptible Populations

Anyone at any age can get sepsis, but it is more common in infants, elders, and those who are ill or weakened. About 2 of every 3 patients who develop sepsis already have another significant illness. It can be caused by simple infection such as an insect bite, urinary tract infection, or pneumonia. People with chronic health conditions such as diabetes, cancer, kidney and liver disease; those with suppressed immune systems (from chemotherapy, AIDS, long-term steroid use); and patients with implanted devices or endotracheal tubes are at increased risk of developing sepsis (Neviere, 2013a). A recent study reported that septic shock is the most common cause of death in noncoronary intensive care units, and the tenth leading cause of death overall in high-income countries (Schulte et al., 2013).

Test Your Knowledge

Sepsis tends to strike:

A. Unsuspecting healthy young adults.

B. Infants and elders.

C. Overweight middle-aged adults.

D. Pet owners.

Apply Your Knowledge

What nursing actions can you do to decrease the risk of infection in your facility? How well do you don and take off isolation gowns/gloves between patients? How well do you wash your hands between patients? What special bundles are you using for ventilated patients (eg, VAP protocol)?

Answer: B

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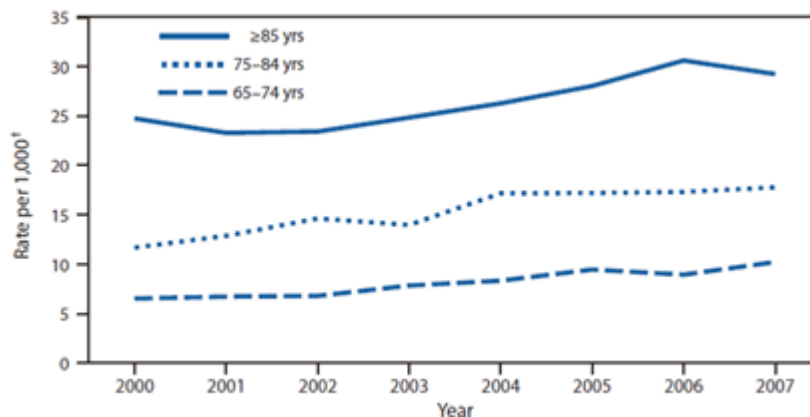
Hospitalizations per 1000 Americans for sepsis in three different age groups, during the years 2000 to 2007. Comparing the three lines, the risk of getting sepsis increases with age: people older than 85 years are 5 times more likely to be hospitalized for sepsis than are people aged 65–74 years. Source: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

The Surviving Sepsis Campaign

Because of the high incidence of sepsis and poor clinical outcomes, national and worldwide healthcare systems have petitioned for guidelines. The **Surviving Sepsis Campaign (SSC)** is a global effort to improve the care of patients with severe sepsis and septic shock. The campaign was launched in 2002 by the Society of Critical Care Medicine, the European Society of Intensive Care Medicine, and the International Sepsis Forum, with their latest update in 2015. The objective of the campaign was to develop and disseminate evidence-based guidelines so that the knowledge obtained from clinical trials could be applied to bedside practice. The goal was to reduce death from severe sepsis and septic shock by 25%.

Historically, invasive management and aggressive resuscitation of the septic patient occurred in the intensive care unit (ICU); however, sepsis is now recognized as an overwhelmingly time-critical disease, requiring early initiation of care in the emergency department (ED), with subsequent transfer to the ICU (Perman et al., 2012).

The Surviving Sepsis Campaign developed guidelines known as **early goal directed therapy (EGDT)** to increase sepsis awareness and to direct treatment. Recommendations are classified into three groups: (1) those directly targeting severe sepsis, (2) those targeting general care of the critically ill patient and considered high priority in severe sepsis, and (3) pediatric considerations. The guidelines are intended to be best practice guidelines and not definitive standards of care (Buckman, 2013). In addition, in 2015 the Centers for Medicare and Medicaid Services (CMS) presented a new inpatient reporting program called **SEP-1**, requiring hospitals to report the **bundle measures** to help hospital staff focus on these disease progression-halting measures (Schorr, 2016).

Treatment begins with 3-hour and 6-hour windows (bundles) involving the infusing of large quantities of intravenous crystalloid fluids, stabilizing ventilation and circulation, beginning diagnostic studies, administering antibiotics, and searching for the source of infection. When this initial work is done and patients have stabilized, they are given supportive critical care. If the patient has not improved or continues to deteriorate, treatment must be re-evaluated quickly. The average patient who has sepsis spends 2.5 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.

Although it has been shown that adherence to the EGDT protocol saves lives, consistent implementation has been challenging. Noncompliance with 3- and 6-hour sepsis bundles has been demonstrated to increase in-hospital mortality for septic patients, while compliance with the resuscitation bundle, even if extended from the recommended time frame, decreases mortality (LaRosa et al., 2012).

3-hour bundle

- Measure the patient's lactate level.

- Obtain blood cultures before antibiotic administration.

- Administer broad-spectrum antibiotics.

- Administer 30 mL/kg crystalloid for hypotension or a serum lactate of 4 mmol/L or higher.

    6-hour bundle

- Give vasopressors to keep MAP >65 mm Hg (if hypotension doesn't respond to fluid resuscitation).

- Reassess volume status and tissue perfusion if hypotension persists and MAP is <65 mm Hg.

- Re-measure lactate level if the initial level was elevated.

Test Your Knowledge

The Surviving Sepsis Campaign developed guidelines known as early goal directed therapy (EGDT). Recommendations were classified into three groups. Which one of the following is **not** one of the groups?

    A.   Those directly targeting severe sepsis.
    B.   Those targeting general care of the critically ill patient with severe sepsis.
    C.   Those targeting pediatric patients.
    D.   Those targeting the elderly.

Apply Your Knowledge

Q: In our earlier scenario, what components of the 3- or 6-hour bundle actions were taken?

A: None of the 3-hour bundle recommendations were completed because the diagnosis was simple pneumonia. Due to the delay in arriving to a med/surg floor, the antibiotics were not started until 5 hours later and no blood culture was completed prior to the first dose.

Answer: D

Pathophysiology of Sepsis

Triggering Infections

Sepsis does not arise on its own. It stems from another medical condition, such as an infection in the lungs, urinary tract, skin, abdomen (eg, appendicitis) or other part of the body. Invasive medical procedures like the insertion of a vascular catheter can introduce bacteria into the bloodstream and bring on the condition (NIGMS, 2013).

Many different types of microbes can cause sepsis, including bacteria, fungi, and viruses, but bacteria are the most common culprits. Severe cases often result from a body-wide infection that spreads through the bloodstream, but sepsis can also stem from a localized infection (NIGMS, 2013).

The causative organisms for sepsis have evolved over many years. Originally sepsis was described as a disease specifically related to Gram-negative bacteria. This is because sepsis was thought to be a response to endotoxin—a molecule felt to be relatively specific for Gram-negative bacteria. In fact, some of the original studies of sepsis showed that Gram-negative bacteria were among the most common causes of sepsis. This resulted in a number of trials that focused on Gram-negative therapies, and even highly specific therapies for endotoxin, which were felt to be potentially useful treatments for sepsis.

It is now recognized that sepsis can be caused by any bacteria, as well as from fungal and viral organisms. More recent epidemiology studies show that Gram-positive organisms superseded Gram-negatives in the early to mid-1980s as the most common cause of sepsis in the United States. According to the most recent estimates, there are approximately 200,000 cases of Gram-positive sepsis and approximately 150,000 cases of Gram-negative sepsis each year (Martin, 2012).

While bacterial causes of sepsis have increased, fungal causes of sepsis have grown at an even more rapid pace. This may represent a general increase in **nosocomial** (hospital-acquired) cases of sepsis, or it may reflect our effective treatment of bacterial infections, which thus allowed fungal infections to grow without competition. While there has been an overall increase in the number of fungal nosocomial infections, we have also observed shifts away from the most common *Candida albicans* organism to the more recalcitrant torulopsis, glabrata, and krusei subspecies (Martin, 2012).

Test Your Knowledge

Which is correct regarding the relationship between sepsis and systemic inflammatory response syndrome (SIRS)?

   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.

Answer: D

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

- Lungs
- Abdomen
- Kidney
- Bloodstream (Mayo Clinic, 2013)

Obviously, most infections do not trigger a septic reaction. Two people can have infections in the same tissues, 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 causative 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 normal flora bacteria are also the most common causes of sepsis suggests that sepsis is most readily triggered in people who have weakened antimicrobial defenses. Whereas the normal flora are usually a help to our body's digestive system, the bacteria can become deadly when the body isn't able to keep the normal flora controlled.

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 & Suffredini, 2009).

Test Your Knowledge

Commensal bacteria (normal flora):

- A.   Rarely cause sepsis.
- B.   Are notorious for causing sepsis.
- C.   Rarely infect immunosuppressed patients.
- D.   Are not needed in the body.

Apply Your Knowledge

Q: In our case scenario, it is discovered that Nancy Murphy consumes alcohol and one pack of cigarettes daily and lives alone on limited income. Her nutrition status has been poor. How could her nutritional status impact the normal flora and development of sepsis?

A: With poor nutrition and daily alcohol and cigarette intake, the body's ability to fight infection lessens. The respiratory compromise from smoking also puts her at risk to fight the respiratory pneumonia, placing her at great risk for developing sepsis.

Answer: B

Spread of the Inflammatory Reaction

Normally, an inflammatory reaction remains localized, but a septic reaction travels via the vascular system to spread inflammation throughout the body. In sepsis, pro-inflammatory molecules can be found in high concentrations throughout the blood stream (Munford, 2008).

The body's immune system reacts to an invading organism in several ways. The initial and appropriate response to an infection is called the *innate immune response*. It is activated immediately, is not specific to any antigen, and reacts similarly to a variety of organisms. The *adaptive immune response* requires some time to react to an infection and **it attacks only the pathogen that induced the response** (Schulte et al., 2013). The first innate immune response in the body is like a general sending out the quick masses of army men to fight an invader, and the adaptive immune response takes the general time to develop a more specific strategy such as sending out specific snipers to fight the now-identified invader.

Your immune system is absolutely amazing! During the innate immune response, blood vessels dilate in the infected tissue to increase circulation, which allows white blood cells (WBCs) to arrive at the scene of attack. The activation of this first line of cellular defense results in an excessive release of cytokines and other inflammatory regulators, which causes massive vasodilation and hypotension (Schulte et al., 2013). Increased tissue permeability also allows the helpful WBCs and immune cells to enter tissue and identify the invading pathogens. Sepsis has been shown to develop when the innate immune response becomes amplified and dysfunctional, leading to an imbalance between pro-inflammatory and anti-inflammatory responses. It is the innate immune response that plays a major role in sepsis pathophysiology.

Cytokines regulate a variety of inflammatory responses, including the migration of immune cells to the infection, which is a crucial step in containing a localized infection and preventing it from becoming systemic. In the army analogy, the cytokines are like special forces, which go into the invading camp and identify the enemy. However, an uncontrolled cytokine release may lead to vasodilation, increased capillary permeability, and breakdown of normal epithelial cell walls that ideally serve as protective barriers. The resulting leakage syndrome can cause hypotension, hemoconcentration, macromolecular extravasation, and edema, which are frequent findings in septic patients.

Whereas normally the epithelium is a protective barrier, if injured it allows pathogens and their products to further invade the host, to disturb regulatory mechanisms, and, ultimately, to cause organ dysfunctions. Evidence has indicated that immune and inflammatory responses are tightly interwoven with physiologic processes within the human host (eg, coagulation, metabolism, neuroendocrine activation). An inflammation-induced disruption of the coagulation system, for instance, significantly worsens the effects of sepsis and can result in lethal **disseminated intravascular coagulation (DIC)** (Schulte et al., 2013).

Traditionally, sepsis was viewed as an excessive systemic pro-inflammatory reaction to an infection. More recently it has been proposed that the early phase of hyper-inflammation is followed or overlapped by a prolonged state of immunosuppression, referred to as **sepsis-induced immunoparalysis**. This immunoparalytic state is characterized by impaired innate and adaptive immune responses and may play a central role in tissue damage, multiple organ failure, and death induced by sepsis (Schulte et al., 2013). What causes the immunosuppression is still being researched and may include nutritional status, toxins in the body, and genetics.

Pro-Inflammatory Molecules in the Circulation

Three components of the body's response to infection are the cytokines, activated complement, and activated coagulation factors. All of these components are inherently part of the body's nature defense mechanism and, when functioning properly, protect the body beautifully from foreign pathogens. You are quite a miracle when all systems work correctly. Given the fact that there are 10 times more microorganisms on your body than cells in your body, it is amazing we all aren't sick (Wenner, 2007). When the components and process becomes dysfunctional, sepsis can occur.

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. Think of them as the alarm system for the body to announce when there is an invader.

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 by sending out the alarm for war against invaders that may not be in those tissues (Abbas et al., 2011).

Test Your Knowledge

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.

Answer: A

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. These initial processes take place in all types of infections from small facial blemishes those that become 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, 2013a). Your body is quite amazing in that this is happening automatically while you are reading this course. Your body fights pathogens all day, every day, and mostly you will never be aware of it because this system works so brilliantly.

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 deposit of fibrin by the coagulation cascade into a sticky mesh that 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, 2013a).

Test Your Knowledge

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.   Answer: D

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 Neviere (2013a):

> 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 bloodborne 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 into 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 peak invader-destroying activity and then the activity automatically tapers off and ends.

The inflammatory response must be terminated because it is imprecise and it causes collateral damage by injuring or destroying 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 cleanup 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, 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-balance, with the pro-inflammatory processes dominating.

Test Your Knowledge

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.

Answer: C

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, making it more likely that small clots will form throughout the vascular system (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. Protein C is your body's natural anticoagulant and, when lacking, puts the patient at risk for clotting.
>
> Source: Bauer, 2013.

Test Your Knowledge

Protein C, which helps to control coagulation and is unusually low in patients with sepsis, is also known as C-reactive protein.

    A.   True

    B.   False

Answer: B

If unopposed by protein C-dependent blockades, the continuous stimulation of the coagulation system will sometimes lead to 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 restraints 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, 2013a).

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, 2013a). As in any war, the enemy also has strategies, and in the case of human biologic warfare within our bodies, bacteria produce chemicals that can enhance our release of cytokines. Generally cytokines help to notify that an enemy (pathogen) has entered our body; however, when they are released in larger quantities they become destructive and create an over-reactive response. It's a clever strategy of the enemy to scatter our own soldiers, creating chaos within our ranks.

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.

Effects of the Spreading Inflammatory Reaction

The effects of spreading inflammatory reaction include endothelial damage, organ damage, adult respiratory distress syndrome (ARDS), progression to shock, and progression to death.

Endothelial Damage

The endothelium is involved in the control of vascular tone, platelet reactivity, coagulation, and permeability. The endothelial cells that line blood vessels, called **vascular endothelial cells**, are the gatekeepers between the bloodstream and the body's tissues. A healthy vascular endothelium protects against excessive/abnormal inflammation and coagulation. The transition from a normal to a dysfunctional endothelium is associated with abnormal vasomotor activity, the development of a pro-coagulant surface, and an acceleration of the inflammation process (Bacon et al., 2011). An early indicator of sepsis is damage to these vascular endothelial cells and can manifest in hypotension.

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 system. 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, which is what creates redness and inflammation as signs of infection (Ely & Goyette, 2005).

Test Your Knowledge

An early indicator in all types of sepsis is damage to the:

- A.   Vascular endothelial cells.
- B.   Skin epithelial cells.
- C.   Red blood cells.
- D.   T- cells.

Answer: A

Organ Damage

Sepsis can evolve to **multiple organ dysfunction syndrome (MODS),** which has a mortality rate of between 30% and 50% (Nesseler, 2012). Damage to the vascular endothelium causes 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 failure, and the risk of the patient dying doubles for each organ that fails (Shapiro et al., 2010).

Lungs

The lungs are usually an early casualty in sepsis, regardless of the location of the initial infection. The surface area of the vascular endothelium of the lungs is large, and when a septic reaction begins disrupting endothelial areas in the body the lungs are likely to suffer significant damage. The surface area of one lung has been said to be the size of a tennis court! This can help you visualize the potential surface area for gas exchange but also potential tissue damage.

Regions of the lung with damaged endothelia become filled with neutrophils and macrophages, as if the dead soldiers of a lost battle spread across a battlefield. 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 damaged in sepsis. As a protective mechanisms, your amazing lungs have the ability to close off circulation to any damaged areas to conserve energy. HPV is a protective mechanism that normally redirects arterial blood away from any nonfunctioning parts of the lung to better ventilated areas (Wang et al., 2012). 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, 2013a).

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, as if a white out in a snow storm. Gas exchange is reduced, and the patient becomes dyspneic and hypoxemic.

One characteristic of hypoxemia in ARDS is a low arterial oxygen level that remains low despite 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.

Source: 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 hypoxemia. The lungs become fluid-filled and poorly compliant, making breathing more difficult. A chest x-ray will show new bilateral diffuse or 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%. The most frequent etiology is pneumonia, followed by nonpulmonary infections.

There is no specific preventive treatment against the development of ARDS in patients with sepsis. Novel therapies are being studied, but no promising results have been reported. It seems that early detection of patients with sepsis who are at risk of developing ARDS is one way to achieve better results in the earliest phase. Indeed, one of the most important preventive strategies is to ensure adequate management of sepsis, including source control and early appropriate antibiotic therapy (de Haro, 2013).

Heart

In a patient without pre-existing cardiac problems, the heart can generally endure a bout of sepsis. 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.

As the sepsis continues however, 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 partly compensates for the heart's decreased pumping power. In this way, the cardiac output (blood volume pumped per minute) can remain fairly constant or even increase during a bout of sepsis. In a patient with existing cardiac problems, however, the heart is not as able to endure this stress, often causing complete heart failure.

Kidneys

Like the lung, kidney 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, like 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, which can eventually lead to acute renal failure (Neviere, 2013a).

Gastrointestinal Tract

The spreading hypoperfusion of sepsis limits the oxygen supply to the intestines. Without oxygen, anaerobic metabolism is activated releasing ketones and lactate, which causes a drop in pH 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 spreading throughout the rest of the body. This is why the normal flora, which once was helpful to the body, can become the enemy.

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 then develop paralytic ileus (Neviere, 2013a).

Liver

One of the main functions of the liver is clearance of infectious agents and their products, but sepsis can induce liver damage. Just as sepsis destroys the endothelial cells of all organs, sepsis damages hepatocytes and the hypotension through the body can disrupt blood flow to the liver itself, creating hypoxia and cell death. The sepsis-induced liver dysfunction leads to a spillover of bacteria, bacterial toxins, and debris into the circulation. Elevated liver enzymes and coagulation defects may occur. A decreased ability to excrete toxins such as ammonia can lead to encephalopathy (Nesseler et al., 2012).

Nervous System

In sepsis with so many chemicals and molecules of inflammation in the bloodstream, the brain can become toxic. Sepsis often causes acute brain dysfunction, characterized by fluctuating mental status changes, inattention, and disorganized thinking. The effects on the brain are caused by both inflammatory and non-inflammatory processes, which may induce significant alterations in vulnerable areas of the brain (Sonneville, 2013). The problems begin when circulating inflammatory molecules disrupt the endothelium of the blood vessels along the **blood–brain barrier (BBB).** The leaky BBB 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 situation, neurons shut down and cerebral functions slow.

Brain dysfunction during sepsis is frequently complicated with other factors from previous conditions including withdrawal syndrome, drug overdoses, and severe metabolic disturbances. Currently, the treatment of sepsis-associated encephalopathy consists mainly of general management of sepsis and prevention of aggravating factors, including metabolic disturbances, drug overdoses, anticholinergic medications, withdrawal syndromes, and Wernicke's encephalopathy caused by thiamine deficiency (Sonneville et al., 2013).

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 & 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 in 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 which cause hypotension:

- High levels of lactic acid can cause arterial muscles to be unable to respond when stimulated.
- Sepsis suppresses the release of vasopressin (ADH), a pituitary hormone that, among other functions, maintains arterial constriction.

- Sepsis causes endothelial cells to produce excess nitric oxide, which is a vasodilator. (Shapiro et al., 2010)

Progression to Death

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).

Test Your Knowledge

Death from sepsis is generally the result of:

    A.   Kidney failure.

    B.   Multiple organ failures.

    C.   Pneumonia.

    D.   Lactic acidemia.

Apply Your Knowledge

Q: What additional risk factors did our case study patient have for sepsis?
A: She had additional toxins in her body from daily cigarette and alcohol use, which compounded the stress and infection of pneumonia.

Answer: B

Diagnosis of Sepsis

Severe sepsis and septic shock are unfortunately common, complicated and deadly conditions within the same pathophysiologic spectrum. If a clinician believes that a patient is exhibiting SIRS secondary to infection, that patient has sepsis. If that same patient has signs or symptoms of organ dysfunction, then that patient has severe sepsis. **Septic shock** is then characterized by overall tissue hypoperfusion, tissue hypoxia, or general hypotension that fails to respond to fluid resuscitation (Tannehill, 2012).

The initial management of sepsis requires rapid identification of sepsis. Delay in diagnosis and treatment often results in rapid progression to circulatory collapse, multiple organ failure, and eventual death. Emergency department triage systems are designed to classify patients by severity of illness, with an initial set of vital signs, chief complaint, and focused physical exam. During the first encounter with the healthcare delivery system, much information can be gleaned with respect to the presence or potential for the evolution of sepsis to septic shock. However, a definitive diagnosis of sepsis can be difficult (Perman et al., 2012).

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

It is important to stress that few if any patients in the early stages of the inflammatory responses to infection are diagnosed via the four SIRS criteria. Not all individuals who have SIRS criteria are septic and not all patients who are septic meet the SIRS criteria. The signs are non-specific and each sign can be produced by a wide range of causes. There is much overlap in the initial hemodynamic alterations with disease entities such as burns, trauma, and pancreatitis, and clinical judgment must be used in order to accurately diagnose the septic patient (Perman et al., 2012; Herlitz et al., 2012).

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 a simple 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. First-line emergency care practitioners should perform a thorough physical exam (Perman et al., 2012).

Test Your Knowledge

The best diagnostic tool for identifying sepsis is:

    A.   The patient's mean arterial pressure (MAP).

    B.   The patient's blood level of procalcitonin.

    C.   The patient's C-reactive protein (CRP) blood level.

    D.   Clinical experience by identifying signs and symptoms.

Answer: D

Clinical Signs

Potential clinical signs of sepsis are shown in the following box.

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: hypothermia, <96.8°F/36°C; or fever, >100.4°F/38.3°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 (>20 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 with normal = 0.5-2.2 mmol/l)
    - Unexplained base deficit >5.0 mEq/l (normal = <3.0 mEq/l)
- Blood gases
    - Hypercapnia ($PaCO_2$ >65 mm Hg [normal = 33–44 mm Hg] or $PaCO_2$ >20 mm Hg above patient's baseline)
    - Hypoxemia (PaO_2/FIO_2 <300 or mixed venous oxygen saturation (SVO_2) <70% [normal ~75%])
- Blood components
    - Abnormal white blood cell count (WBC)
- Leukocytosis (WBC count >12,000 /mm^3 with normal = 4,500–11,000 /mm^3]) **or**
- Leukopenia (WBC count <4000/mm^3 with 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 = 30–42 s])

- 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; Wang et al., 2012).

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 elderly, and this demographic brings with it a caution about using fever to recognize sepsis. Elderly 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).

Body tissues need more oxygen 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. The body attempts to compensate for vasodilation and decreased intravascular fluid volume by increasing the heart rate (Ely & Goyette, 2005).

Tachypnea is often the first detectable clinical sign of developing sepsis for several reasons. Rapid breathing can be caused by fever, lactic acidosis, pulmonary edema, and because the lungs are the most common site of infection. In addition, the lung is often the first organ to undergo dysfunction during sepsis due to its early involvement in the inflammatory process. This can lead to acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) (Assenzio & Martin-Conte, 2012).

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 but 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 & 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 ARDS develops, a chest x-ray 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 usual. 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 because the vasculature has lost the ability to maintain its tone by responsive arterial constriction.

Source: Kress & 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 (Jui, 2010).

* * *

Finally, a full serum chemistry and urinalysis should be done.

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, antithrombin III, and lactate (Jui, 2010). Blood cultures should be drawn **before** antibiotics are administered (Dellinger et al., 2013b).

Red Blood Cells

Poor tissue perfusion is a hallmark 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 declines during sepsis because 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 called bands (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 (Munford, 2008).

Protein C is a natural anticoagulant factor that helps to counteract the coagulation cascade. A low blood concentration of activated protein C is typical of sepsis, because the cytokines that are released in the inflammatory condition 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).

Lactate

Recent attention has focused on the topic of **biomarkers** (measurable characteristics used as indicators of a disease state). Serum lactate has been the most studied. Lactic acid is a product of cell metabolism and is produced by the breakdown of carbohydrates when oxygen levels are low. Whether it is caused by poor perfusion or an impaired clearance secondary to organ dysfunction, multiple studies have shown that elevation in serum lactate is an effective marker to measure the risk of severe sepsis. Studies have demonstrated that elevations in serum lactate without hypotension were associated with increased mortality in patients who present to the ED with severe sepsis. **Recent studies suggest that serum lactate may perform well as a screening test in the medical decision-making process regarding early ED management and disposition of the septic patient** (Perman et al., 2012).

As early as 1964 it was proposed that serum lactate measured during critical illness correlated with adverse outcomes. Another study in a group of patients with mixed critical illness showed that individuals with a lactate of at least 4 mmol/l had a mortality rate of 87%. This finding was further validated in 1994 and is now suggested by the Surviving Sepsis Campaign as an inclusion criterion for the 3-hour and 6-hour bundles for septic patients. This can help identify and treat severe sepsis patients earlier in their clinical course so as to halt the inflammatory cascade and reverse perfusion abnormalities. Lactate should be re-measured within the first 6 hours of treatment to assess for normalization of levels after oxygen, antibiotics, and fluid support are given (Dellinger et al., 2013b).

Microbiologic Analysis

We have seen that 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, about 70% of the microbes found are bacteria.

Source: James Heilman, Wikimedia Commons.

Test Your Knowledge

When it is possible to identify a microbe causing sepsis, the microbe is most often a:

A. Virus.

B. Fungus.

C. Bacterium.

D. Protozoan.

Answer: C

Cultures should be taken of all other potentially infected sites. Despite having a negative result, cultures of the bloodstream should be taken prior to administration of antibiotics (Dellinger et al., 2013b). 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 general antibiotics. Therefore, as soon as culture samples have been taken, patients are started on wide spectrum antibiotics, with the plan of reassessing the effectiveness daily and customizing the antibiotic once the cultures are available.

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 nephrotoxic antibiotics. For decades, scientists have been trying to find a rapid laboratory 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 & 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 & 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 signs of 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 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 aside from the signs and symptoms of the patient's other problems.

For these reasons, the differential diagnosis for sepsis is broad, as seen in the following box.

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

Source: 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.

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 present with tachycardia, tachypnea, fever, and a high white blood cell count (Gaieski, 2013). A key sign in sepsis is hypotension that cannot be reversed with fluids alone.

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). Two sets of blood cultures should be drawn with the initial labs and prior to administration of antibiotics.

Test Your Knowledge

Septic shock:

    A.   Is caused by cardiac dysfunction such as heart failure or myocardial infarction.

    B.   Presents with hypotension that cannot be reversed by fluid resuscitation alone.

    C.   Typically presents with low blood lactate levels, low blood concentrations of CO_2, and polyuria.

    D.   Is treated only after immediate laboratory testing to determine the causative organism.

Answer: B

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 strangely negative. Staphylococci produce exotoxins, compounds that trigger inflammation directly. 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.

Source: Schwartz, 2011.

Test Your Knowledge

Toxic shock syndrome is:

A. Severe staphylococcal bacteremia but without shock.
B. Staphylococcal bacteremia typically diagnosed by positive blood cultures.
C. A form of septic shock triggered by bacterial toxins.
D. A rapid-onset sepsis causing severe lung injury, pulmonary edema, and hypoxemia and requiring mechanical ventilation.

Apply Your Knowledge

Q: What are the current recommendations for patient education in the use of tampons?
A: change the tampon every 2-4 hours and don't leave tampons in over night.

Answer: C

Differential Diagnosis

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

- 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

Source: Gaieski, 2013.

Treatment of Sepsis

Treatment ensues with resuscitating the patient, followed by a search for the infection, empirical administration of broad-spectrum antibiotics, control of the septic cause if possible, and a turn to sepsis-specific medications following blood cultures.

Resuscitate the Patient

Once septic patients develop macrovascular shock (refractory hypotension) or microvascular shock (elevated lactate), they are on the steep part of the mortality curve and immediate identification and intervention is critical to avert rapid deterioration and death.

Sweet et al., 2012

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 reduced mortalities and ICU stays. The EGDT protocol sets specific target values of critical physiologic parameters toward which the treatment procedures aim (Gutovitz et al., 2011). The sepsis guidelines assume that all recommendations will be overseen and tailored to the individual patient by experienced emergency and critical care physicians.

Two treatment bundles are recommended by the Surviving Sepsis Campaign to accomplish the following goals during the first 6 hours of resuscitation of sepsis-induced hypoperfusion (Dellinger et al., 2013b; Buckman, 2013):

- Central venous pressure (CVP) = 8–12 mm Hg
- Mean arterial pressure (MAP) = ≥ 65 mm Hg
- Urine output ≥ 0.5 ml/kg/hr
- Superior vena cava oxygenation saturation ($ScvO_2$) or mixed venous oxygen saturation (SvO_2) 70% or 65%, respectively
- Normalization of lactate in patients with elevated lactates

Time Zero and Sepsis Bundles

Patients with septic shock require early and vigorous resuscitation with an integrated approach directed to rapid restoration of systemic oxygen delivery and improvement of tissue oxygenation. The first priority is stabilization of the airway and breathing with supplemental oxygen and, if necessary, institution of mechanical ventilation. Once hypoperfusion is recognized, early restoration of perfusion is necessary to limit secondary organ dysfunction and reduce mortality (Boodoosingh et al., 2013).

The 2012 Surviving Sepsis Guidelines include recommendations for a bundle to be completed within the first 3 hours and a bundle to be completed within the first 6 hours of recognition of severe sepsis or septic shock.

Since treatment for the septic patient needs to be started immediately upon recognition, and because many tasks must be done within certain time frames, **time zero** is when the clock begins after diagnosing the patient with sepsis.

Although time zero may be defined differently in individual hospitals, according to the Surviving Sepsis Campaign performance improvement initiative:

- Time of triage in the ED should be used as time zero in order to maximize the bundle's effectiveness for diagnosis as well as treatment.

- The campaign acknowledges "that a percentage of patients may not meet criteria for severe sepsis or septic shock at ED triage" and that "100% compliance for some indicators is not always possible" (Dellinger et al., 2013a).

Test Your Knowledge

In general, time zero for treatment is understood to have begun when the patient first complained of feeling ill.

    A. True

    B. False

<div align="right">Answer: B</div>

The bundle to be completed within **3 hours** of time zero is:

1. Lactate levels should be drawn.

2. Blood cultures should be drawn before antibiotics are given.
   - Do not delay administration of broad-spectrum antibiotics more than 45 minutes for blood culture draw.

3. Broad-spectrum antimicrobial agents should then be administered (within the first hour) that target likely pathogens (bacterial, fungal, or viral).
   - Antimicrobial therapy should be reassessed daily for possible de-escalation.

4. A minimum initial fluid challenge of 30 ml/kg bolus of crystalloid (normal saline) should be given for hypotension or a lactate of 4 mmol/l.
   - More rapid administration and greater amounts of fluid may be needed in some patients.
   - Colloids may be given as part of the fluid challenge if large amounts of crystalloids are required.
   - Avoid hetastarch. (Dellinger et al., 2013a; Buckman, 2013)

The 2012 guidelines recommend further resuscitation of patients with hypotension that persists after the initial fluid challenge or who have blood lactates ≥ 4 mmol/l. This protocol should be started upon recognition of severe sepsis or septic shock. A central venous catheter (CVC) should be placed for central venous pressure (CVP), central venous oxygen saturation readings (ScvO$_2$) and for administration of vasopressors (if needed). A CVC can also be used to infuse IV fluids, medications, blood products, and to draw blood (Schmidt & Mandel, 2016).

The bundle to be completed within **6 hours** of time zero is (Buckman, 2013):

5. Vasopressors should be given for hypotension that does not respond to initial fluid boluses to maintain mean arterial pressure (MAP) of 65 mm Hg.
   - Norepinephrine is recommended as the first-choice vasopressor.

   - Epinephrine is recommended when norepinephrine does not maintain adequate blood pressure.

   - Dopamine is recommended only in selected cases with low risk of tachyarrhythmias.

6. For persistent hypotension despite fluid resuscitation or initial lactate ≥ 4 mmol/l:
   - Measure CVP—resuscitation target is 8–12 mm Hg.

   - Give fluid boluses of 500 ml every 30 min to achieve this goal.

   - Measure ScvO$_2$ (central venous oxygen saturation): resuscitation target is ≥ 70%.
     - Once CVP and MAP are at goal, the clinician's attention should then turn to the central venous oxygen saturation, ScvO$_2$. The clinician must decide between the addition of dobutamine and transfusing blood if the ScvO$_2$ is less than 70%. For a hematocrit less than 30%, blood is transfused. (Boodoosingh et al., 2013)

7. Re-measure lactate if initial lactate is elevated (>2 mmol/l); goal is normalization of lactate. (Buckman, 2013)

The Surviving Sepsis Campaign guidelines recommend "bundles" of measures that must be completed in:

A. Three and six seconds from time zero.

B. Three and six minutes following time zero.

C. Three and six hours from time zero.

D. Three and six shifts following time zero.

Apply Your Knowledge

What is your facility doing to increase awareness of the bundles for sepsis? How can you being an advocate to improve compliance?

Answer: C

Recommendations During Resuscitation

Attention is directed to respiration, blood volume, blood pressure, cardiac output, and septic shock.

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. 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 signs of poor tissue perfusion, intravenous fluids are begun and crystalloids are the initial fluids of choice. 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. Colloids may be added when large amounts of fluids are needed. **Hetastarch is no longer recommended** (Buckman, 2013).

Fluid is given rapidly in boluses of 500 ml of normal saline to achieve a minimum of 30 ml/kg, with blood pressure, tissue perfusion, and pulmonary edema assessed before and after each bolus. Fluids are administered as long as there is hemodynamic improvement and until the target values are met, initially aiming for a central venous pressure of 8 mm Hg (12 mm Hg in mechanically ventilated patients). Patients with severe sepsis or septic shock should have a central venous catheter placed for these readings. Fluids are stopped if pulmonary edema develops or when no improvement in the target values is seen.

Test Your Knowledge

Initial fluid resuscitation for sepsis:

A. Attempts to improve tissue perfusion with large volumes of intravenous crystalloids.

B. Provides electrolyte-rich fluid by mouth to counteract severe dehydration.

C. Should be delayed until 6 hours after the administration of antibiotics because it dilutes their concentration in the circulation.

D. Has been superseded by the early administration of corticosteroids.

Answer: A

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. Norepinephrine is the recommended first-line vasopressor. Epinephrine can be used when an additional agent is needed to maintain blood pressure. Dopamine should only be used in highly selected patients with a low risk of tachyarrhythmias (Buckman, 2013). Vasopressors are typically given through a central venous catheter (Shapiro et al., 2010).

Did You Know . . .

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., 2013b; Morrell et al., 2009).

Once a staple of critical care monitoring, pulmonary artery catheters (Swan-Ganz catheters) are being used less often and more cautiously (Weinhouse, 2013). Some clinicians recommend against the routine use of pulmonary artery catheters for sepsis, severe sepsis, or septic shock (Schmidt & Mandel, 2013).

Test Your Knowledge

Swan Ganz catheters are no longer a staple of critical care monitoring.

    A. True
    B. False

Apply Your Knowledge

Q: Why are pulmonary artery catheters (Swan Ganz catheters) being used less often?
A: Once popular and widely used in the 1970s to 1990s, studies show many complications (eg, pulmonary bleeding), questionable benefits, and unreliable measurements from using pulmonary artery catheters. What have you seen in your ICU? The transesophageal echography can show more reliable results of heart function.

Answer: A

Cardiac Output

If the oxygenation saturation remains low and if it appears that cardiac output is reduced, consider using dobutamine (an ionotrope) 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., 2013b; Schmidt & Mandel, 2013).It is recommended that cardiac output not be pushed above normal levels.

Septic Shock

Septic shock can be recognized by its refractory hypotension, which means that despite aggressive fluid resuscitation the patient's blood pressure remains hypotensive. The resuscitation of patients in septic shock should continue until all target values are met (eg, lactate and pH and oxygenation), not just the blood pressure target. 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., 2013b; Gaieski, 2013).

Search for the Infection

Targets during the initial search for an infection include:

- Two or more blood culture samples:
  - One percutaneous
  - One from each vascular access device that has been in place >48 hr
- Culture samples from other potentially infected sites (Dellinger et al., 2013b)

Identify the Microbes

Beginning antibiotic therapy is a high priority: delays increase the risk of mortality. Antibiotics or other anti-infectives should be given within 1 hour of recognition of sepsis (Buckman, 2013; Morrell et al., 2009).

Briefly Search for the Source

A quick, wide-ranging physical examination is the best way to begin the search for an infection. The source is sought and diagnosed or excluded as rapidly as possible. Intervention for source control should be done within 12 hours when the patient is able to tolerate it (Buckman, 2013).

Surgical sites are 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 laboratory (Dellinger et al., 2013b).

Give Antibiotics Empirically

Recommendations for the initial administration of antibiotics are:

- 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
    - Good tissue penetration into the probable site of the infection
- Use a combination of antibiotics for:
    - Pseudomonas
    - Neutropenic patients
- Antifungals or antivirals should be used if fungal or viral source is suspected
- Reassess the antibiotic regimen daily (Dellinger et al., 2013b)

Test Your Knowledge

Antibiotics are a key tool in treating sepsis. They should be given:

   A.   As soon as sepsis is suspected and before any other treatment begins.

   B.   As soon as a patent airway and appropriate ventilation are ensured.

   C.   Along with intravenous fluids during the initial resuscitation.

   D.   As soon as basic patient data are collected and preferably right after blood cultures have been drawn.

Answer: D

Initial Drugs

It is recommended that initial empiric anti-infective therapy include one or more drugs that have activity against all likely pathogens—bacterial and/or fungal or viral (Dellinger et al., 2013b).

As soon as all culture samples have been taken, patients should be started on an intravenous antibiotic regimen. Anti-infective administration should not be delayed more than 45 minutes to collect the cultures and should be started within 1 hour of recognition of sepsis. Rapid administration of appropriate anti-infective agents has been shown to reduce mortality by 10% to 15% in patients with severe sepsis, whereas a delay of only 1 hour is enough to raise mortality rates (Shapiro et al., 2010).

The choice of anti-infectives 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 or other anti-infectives should be effective against Gram-positive bacteria, Gram-negative bacteria, and likely fungi and viruses. **Methicillin-resistant _Staphylococcus aureus_ (MRSA)** is a growing cause of sepsis in the community as well as among hospitalized patients. For sepsis of unknown origin, vancomycin is recommended until MRSA is excluded as the cause of the sepsis (Schmidt & Mandel, 2013).

If pseudomonas is unlikely, then vancomycin should be combined with a third-generation cephalosporin, carbapenem, or extended-spectrum carboxypenicillin.

Test Your Knowledge

Empiric antibiotics are:

A. Also known as fourth-generation antibiotics.
B. Given before the exact microbes causing sepsis are identified to at least begin fighting the infection.
C. Coated antibiotic tablets to prevent irritation of the stomach.
D. Administered to SIRS patients as a prophylaxis.

Answer: B

Subsequent Drugs

Usually antibiotics are given for 7 to 10 days, although the detailed plan for any individual patient varies (Schmidt & Mandel, 2013). The effectiveness of the patient's antibiotic regimen should be reassessed daily. If microbiology lab results identify the infecting microbe, the antibiotic regimen is tailored for that organism and its particular drug.

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, antibiotics should be stopped (Dellinger et al., 2013b).

Control the Septic Source

Identifying the source of sepsis, called **source control**, is the rapid diagnosis of the specific body site of infection amenable to control measures such as abscess drainage, debridement of infected necrotic tissue, and removal of a potentially infected device. Possible infectious causes include: intra-abdominal abscess, intestinal infarction and/or gastrointestinal perforation, cholangitis, pyelonephritis, empyema, and septic arthritis (Boodoosingh et al., 2012).

When source control is required, minimally invasive interventions are employed—for example, performing percutaneous rather than surgical drainage of an abscess. If less invasive approaches are inadequate or there is uncertainty about the diagnosis, then more aggressive measures should be considered (Boodoosingh et al., 2012; Dellinger et al., 2013b).

When an intravascular access device has been identified as the possible cause of severe sepsis, removal of the device is done only after other vascular access has been established. 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. The 2012 Guidelines recommend that source control be accomplished within 12 hours of diagnosis (Dellinger et al., 2013b).

At other times, however, it is necessary to conduct a quick but thorough search. Here are some search suggestions:

- **Catheters.** All indwelling cannulas, lines, and catheters are potential sources of the infection. 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. An x-ray 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 problems (Shapiro et al., 2010).

- **Abdomen.** Assess the patient for 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). An abdominal x-ray 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 liver 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. Asses women 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 tonsil 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.

- **Skin.** Look for ulcers or cellulitis. Also, look for lesions, petechiae, or rashes that may be clues to the underlying infection.
- **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).

Sepsis-Specific Medications

Unfortunately, there are few medications available to patients already exhibiting sepsis. Corticosteroids are anti-inflammatories that may be useful in the septic patient.

Limited Options

Even after aggressive treatment, the septic patient continues to have an elevated chance of mortality. Scientists have worked with minimal success to find drugs that will reduce the sepsis-specific risks of dying. At this time, a single cure for sepsis does not seem likely. "A deeper understanding of the processes leading to sepsis is necessary before we can design an effective suite of interventions" (Lancet Infectious Diseases, 2012).

According to Lee & 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.

Corticosteroids and Sepsis

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 (Shapiro et al., 2010).

The Guidelines suggest using intravenous hydrocortisone as a treatment for adult septic shock **only** if adequate fluid resuscitation and vasopressor therapy are unable to restore hemodynamic stability. If this is not achievable, the Guidelines suggest intravenous hydrocortisone alone at a dose of 200 mg/dl (Buckman, 2013).

Test Your Knowledge

Because sepsis is an out-of-control inflammatory reaction, corticosteroids:

A.   Have proved an ideal addition to the treatment of mild forms of sepsis.
B.   Would seem to be helpful, but have not proven so in most patients with sepsis.
C.   Are currently used as drugs to prevent sepsis, especially in immune-compromised patients.
D.   Are typically given as an adjunct or booster with empiric antibiotics.

Answer: B

Supportive Therapy of Severe Sepsis

Supportive therapies include blood product administration, mechanical ventilation, sedation, anesthesia and neuromuscular blockade, glucose control, renal replacement therapy, DVT prophylaxis, and good nutrition.

Blood Product Administration

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, red blood cell transfusion should occur only with a hemoglobin concentration of less than 7.0 g/dl (Dellinger et al., 2013b).

Platelets can be given:

- If the platelet count is <10,000/mm^3 in the absence of apparent bleeding **or**
- If the platelet count is <20,000/mm^3 when there is a significant risk of bleeding **or**

- If surgery or invasive procedures are planned, transfusion may occur with platelet counts ≥50,000/mm^3 (Dellinger et al., 2013b)

The Guidelines recommend against the use of erythropoietin for anemia and against the use of fresh frozen plasma (FFP) in the absence of bleeding or planned invasive procedure.

Immunoglobulins

The Guidelines recommend against the use of immunoglobulins and selenium because there is not enough evidence of benefit in severe sepsis (Buckman, 2013).

Mechanical Ventilation

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 & Hall, 2008).

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 30 to 45 degrees helps to prevent aspiration and ventilator pneumonias (Buckman, 2013).

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

Source: Ely & Goyette, 2005.

Extubation

The discontinuation of mechanical ventilation is crucial and should be based on a weaning protocol to assess readiness of successful extubation, reducing the duration and the complications related with it (Boodoosingh, 2012). 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:

- Cough and other airway reflexes working
- Arousable
- Hemodynamically stable (without vasopressor agents)
- No new potentially serious conditions
- Low ventilatory and end-expiratory requirements
- Low FIO_2 requirements that can be met and safely delivered with a face mask or nasal cannula (Buckman, 2013)

If the spontaneous breathing trial is successful, consideration should be given to extubation. 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 & Hall, 2008; Buckman, 2013.

Test Your Knowledge

In septic patients, mechanical ventilation is:

A. Used as a last resort because of the difficulty of weaning patients from dependence on the machine.
B. Needed only when vasopressors are being used to treat hypotension.
C. Commonly needed.
D. Rarely needed.

Answer: C

Sedation, Anesthesia, and Neuromuscular Blockade

The Guidelines recommend:

- Minimal use of sedation during mechanical ventilation
- Avoiding neuromuscular blocking agents in patients without ARDS
- A short course of neuromuscular blockers in patients with ARDS (Buckman, 2013)

Glucose Control

Hyperglycemia is induced by stress and infection, and it is common in critically ill patients, even patients who have no history of diabetes (Schmidt & Mandel, 2013). 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).

The prevalence of hyperglycemia in critically ill patients can be as high as 50% to 75%. Historically, moderate hyperglycemia was considered at best to be an adaptive response to critical illness, and at worst a marker of severity of disease. However, several studies have clearly demonstrated an association between hyperglycemia and mortality in both adult and pediatric nondiabetic critically ill patients (Choong, 2012).

It is recommended that blood glucose levels be kept <180mg/dl for septic patients and that insulin should be used after two consecutive readings that are >180 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) (Buckman, 2013).

Renal Replacement Therapy

Acute kidney injury (AKI), a complex disorder with clinical manifestations ranging from a minimal elevation in serum creatinine to anuric renal failure, is a frequent and serious complication of sepsis in ICU patients. Septic AKI, which accounts for 50% or more of AKI cases in ICUs, is associated with a very high mortality. Although medical practice has advanced in the last decade, the pathophysiology of sepsis-induced AKI is incompletely understood. Current treatments for sepsis-induced AKI including intensive insulin therapy and early goal-directed therapy have been reported to be beneficial; however, there are still no radical treatments to completely treat septic AKI (Choong, 2012).

The Surviving Sepsis Guidelines for 2012 recommend **continuous renal replacement therapies (CRRT)** or intermittent hemodialysis as equivalent therapies in patients with severe sepsis and acute renal failure (Dellinger et al., 2013b). CRRT is continuous extracorporeal blood purification with target replacement fluid rates of 20 to 30 ml/kg/hr. Bicarbonate or citrate-based replacement solutions are used. A 1:1 nursing ratio is employed for all patients on CRRT (Allegretti et al., 2013).

There are currently no drugs that can protect the kidney during an episode of sepsis. The best the clinician can do is to avoid additional 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 (2005), the use of nonsteroidal anti-inflammatory drugs used to treat fever can actually inhibit prostaglandin production and impair the kidney's ability to regulate blood flow and pressure.

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., 2013b). It can take weeks for survivors of sepsis to regain their normal kidney function.

DVT Prophylaxis

Immobile patients are at risk for developing thrombi in the deep veins of their lower limbs with the potential for emboli to the lungs and elsewhere. The pneumonic is often used "Legs to Lungs and Heart to Head, " which is a reminder that a leg DVT will generally move to the lungs and an embolism of the heart will travel to the head. This risk increases in a septic patient, who is likely to be elderly and to have a central venous access device in place. Remember that in patients with severe sepsis the coagulation system is usually headed toward clotting rather than fibrinolysis.

The recommended deep-vein thrombosis prophylaxis for patients with sepsis begins with a combination of low molecular weight heparin (LMWH) and intermittent mechanical compression devices. 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 (Buckman, 2013).

Stress Ulcer Prophylaxis

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 routine for sepsis. More recent meta-analyses suggest that proton pump inhibitors may provide more protection against GI bleed than H2 blockers. 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., 2013b).

Nutrition

A patient with sepsis will be in the ICU for 1 to 2 weeks. Proper nutrition can shorten the stay. Feeding via the gastrointestinal tract is preferred. According to Ely and Goyette (2005):

> 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.

For patients receiving enteral feedings, the head of the bed should be elevated 30 to 40 degrees (Morrell et al., 2009).

Secondary positive outcomes of enteral feedings include (Buckman, 2013):

- Reductions in infectious complications
- Reduced length of mechanical ventilation
- Reduced ICU and hospital stays

The 2012 nutritional guidelines for septic patients include (Buckman, 2013):

- Administer oral or enteral feedings rather than complete fasting or administration of IV glucose within the first 48 hours after diagnosis.
  - Enteral feedings are given through a nasogastric (NG) tube for short-term use or through a tube surgically placed into the stomach
- Avoid full-caloric feedings during the first week. Low dose feedings are recommended of up to 500 calories/day if the patient can tolerate them.
- Use IV glucose and enteral nutrition rather than **total parenteral nutrition (TPN)** alone or TPN with enteral feeding in the first days after diagnosis.

Test Your Knowledge

Combating hyperglycemia by limiting blood glucose levels in septic patients to <180 mg/dl:

- A.   Should be done using insulin.
- B.   Is critical for diabetic patients but not necessary for non-diabetics.
- C.   Will worsen survival rates and should be avoided.
- D.   Should be done by restricting glucose intake.

Answer: A

Body Temperature

Sepsis often produces an abnormal body temperature—either fever (>38°C) or hypothermia (<36°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 watched cautiously, but higher temperatures (>40°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.

Setting Goals of Care

Vincent and colleagues report (2011):

> 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.

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 their desires for continued treatment. It may be in the patient's best interest to provide less-aggressive life-sustaining treatments or to withdraw life-sustaining treatments (Dellinger et al., 2013b).

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 can produce (Dellinger et al., 2013b).

The Guidelines recommend that goals of care and prognosis be discussed with the patient and family and that they be incorporated into the treatment and end-of-life planning. Palliative care principles should be used where appropriate. These goals need to be addressed as soon as feasible, but no later than 72 hours after ICU admission (Buckman, 2013).

The guidelines promote early and repeated care-conferencing with consideration of spiritual and cultural differences. Palliative care includes:

- Pain management

- Symptom control

- Improved patient comfort

- Improved family communication (Buckman, 2013)

Prognoses for Patients with Sepsis

When sepsis becomes severe, it has a high mortality rate even with appropriate care. Estimates of fatality rates (the percentage of patients who die) are as follows:

- Sepsis: 10% to 20%

- Severe sepsis: 20% to 50%

- Septic shock: 40% to 80% (Martin & Wheeler, 2012)

The mainstay in the proper management of sepsis is early recognition of the patient at high risk for death. Early identification of the most critically ill patients allows interventions that can lower 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. The application of severity scores and biomarkers has traditionally been used to score critically ill patients.

Scoring Systems

The most widely applied score is that of the Acute Physiology and Chronic Health Evaluation II (APACHE II) and its revisions, Apache III and IV (Giamarellos-Bourboulis et al., 2012).

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 outcomes.

APACHE is one of a number of objective rating systems currently in use. These measures are helpful in characterizing groups of patients in clinical studies but they are less helpful in making predictions about individual patients.

Source: Liu & Gropper, 2009.

Critical care physicians have developed a number of other ranking systems for comparing the severity of illness of ICU patients. Although the most widely used system is the APACHE classification, 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., 1998)
- Multiple Organ Dysfunction Score (Marshall et al., 1995)
- Logistic Organ Dysfunction System (Le Gall et al., 1996)

To ensure accuracy, all of these scoring systems must be periodically updated to reflect the effects of new technology, standards of care and patterns of practice. A lack of updates in the various systems has often led to an overestimation of mortality (Parsons, 2013).

Importantly, the different types of scores should be seen as additional information, rather than competitive and mutually exclusive. It is possible that their combined use could provide a more accurate indication of disease severity and prognosis. All these scoring systems will need to be updated with time as ICU populations change and new diagnostic, therapeutic, and prognostic techniques become available (Vincent & Moreno, 2010).

Kress and Hall (2008) 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.

Counting Organ Failures

Septic patients with failing organs are at increased risk for dying, and the risk increases as the number of organs fail. 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.

A count of the number of organ failures in a patient with sepsis identifies:

  A.   The patient's current immune status.

  B.   Patients who will benefit from a transplant.

  C.   Those patients with an underlying Gram-negative infection.

  D.   Patients who have a high risk of dying.

Answer: D

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 box shows 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 age

Patient's medical history

- Has a concurrent disease (eg, AIDS, alcoholism, cirrhosis, cancer, liver failure, renal failure)
- Is immunosuppressed
- Is malnourished

Blood pressure

- Persistence of hypotension (systolic BP <90 mm Hg)

Body temperature

- Persistently low temperature (<35.5°C)
- Persistently high temperature (>40°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

- Gram-positive cocci
- Fungi

- Multiple-drug resistant bacteria
  - Nosocomial (hospital-acquired) infection

Blood cells

  - Leukopenia (white blood cell count <4000 cells/mm3)

Blood chemistry

  - Elevated venous lactate level (>1)
  - Reduced blood concentration of activated protein C early in the sepsis

Source: Neviere, 2013 a,b; Avest et al., 2013.

Proactive Steps in Sepsis

Proactive steps include prevention in hospital patients and, failing that, treatment optimization.

Prevention

Most cases of severe sepsis occur in patients who are already hospitalized for other reasons. A recent study found that, in a series of 166 patients with bloodstream infections admitted to an intensive care unit, 82.5% had nosocomial infections (Artero et al., 2012).

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 & 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 antibiotic is administered empirically (Kaki et al., 2011)

Treatment Optimization

Patients with sepsis do better 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 improve their sepsis care. In addition to publishing 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.

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. When the septic response is triggered by an infection, inflammation can be found throughout the entire vascular system 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 in sepsis and blood volume is lost. Under the 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 requires administration of multiple liters of fluid. 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% and can exceed 50% in the sickest patients.

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

The mortality and morbidity of severe sepsis can be improved by effective clinical interventions applied in a timely and systematic manner. Like heart attacks and strokes, sepsis treatment is time-dependent and must be initiated upon recognition of the disease.

Clinical studies have led to a protocol optimizing the diagnosis and treatment of sepsis. This protocol is called early goal directed therapy (EGDT). EGDT should be started when a patient presents to the ED, standard Med/Surg unit or ICU with signs and symptoms of sepsis.

Source control should be accomplished within the first 12 hours when the patient is able to tolerate it. 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 removed.

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

The guidelines also recommend that goals of care and prognosis be discussed with the patient and family and that they be incorporated into the treatment and end-of-life planning. Palliative care principles are used where appropriate. These goals need to be addressed as soon as feasible, but no later than 72 hours after ICU admission (Buckman, 2013).

Sepsis is common: it affects millions of people around the world and kills 1 in 4 (often more) and the incidence of sepsis is increasing. 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 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. 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.

Although *time zero* is defined differently in some hospitals, the Surviving Sepsis Campaign defines it as the time a septic patient is triaged in the ED. The 2012 guidelines recommend two bundles that should be completed within three hours and six hours of time zero.

The bundle to be completed within **three hours** of time zero is (Buckman, 2013):

1. Draw lactate levels.

2. Draw blood cultures before antibiotics are given, but do not delay administration of broad-spectrum antibiotics more than 45 minutes for blood culture draw

3. Broad-spectrum anti-infective agents should then be administered that target likely pathogens (bacterial, fungal or viral)
   - Anti-infective therapy should be reassessed daily for possible de-escalation

4. A 30 ml/kg bolus of crystalloid (eg normal saline) should be given for hypotension or a lactate of 4 mmol/l
   - Colloids may be given if large amounts of crystalloids are required

   - Avoid hetastarch

Once severe sepsis is recognized, a central venous catheter should be placed to measure central venous pressure and central venous oxygen saturation. During the first 6 hours, basic diagnostic data is collected and a brief search for the site of the infection needs to be made. Initial data includes blood work and blood cultures; all possible sites of infection are also cultured.

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%.

The bundle to be completed within **six hours** of time zero is:

5. Vasopressors should be given for hypotension that does not respond to initial fluid boluses to maintain mean arterial pressure (MAP) of 65 mm Hg.

    ▫ Norepinephrine is recommended as the first-choice vasopressor.

    ▫ Epinephrine is recommended when norepinephrine does not maintain adequate blood pressure.

    ▫ Dopamine is recommended only in selected cases with low risk of tachyarrhythmias.

6. For persistent hypotension despite fluid resuscitation or initial lactate ≥ 4 mmol/l:

    ▫ Measure CVP: resuscitation target is 8–12 mm Hg.

    ▫ Give fluid boluses of 500 ml every 30 minutes to achieve this goal.

    ▫ Measure $ScvO_2$ (central venous oxygen saturation): resuscitation target is ≥ 70 %.

      ▪ Once CVP and MAP are at goal, the clinician's attention should then turn to the central venous oxygen saturation, $ScvO_2$. The clinician must decide between the additions of dobutamine versus transfusing blood if the $ScvO_2$ is less than 70%. For a hematocrit less than 30%, blood is transfused. Re-measure lactate if initial lactate is elevated—goal is normalization of lactate. (Boodoosingh et al., 2013)

Test Your Knowledge:

Antibiotics should always be delayed until the source of the infection is located for best outcome.

    A.   True
    B.   False

Answer: B

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Surviving Sepsis Campaign

http://www.survivingsepsis.org/Pages/default.aspx

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Post Test

Use the answer sheet following the test to record your answers.

1. The systemic collapse that occurs in sepsis is called:

    a. Disseminated intravascular coagulation (DIC).

    b. Systemic inflammatory response syndrome (SIRS).

    c. Acute respiratory distress system (ARDS).

    d. Acute inflammatory syndrome (AIS).

2. Severe sepsis, or sepsis syndrome, is:

    a. The stage in which organs begin to fail.

    b. Identified by the failure of more than two organs.

    c. Sepsis that has progressed to suppurating wounds.

    d. Seen when the patient is unconscious from admission to the ED.

3. Septic shock is:

    a. Acute cardiac failure reversible with medication.

    b. Preventable by adequate infection controls such as handwashing.

    c. Acute circulatory failure with refractory hypotension.

    d. Associated with pulmonary collapse.

4. The increase in the number of sepsis cases may be due to:

    a. Recent changes in the definition of sepsis.

    b. An increase in international travel.

    c. Greater use of invasive medical procedures.

    d. Increases in sexually transmitted diseases.

5. Sepsis tends to strike:

    a. Unsuspecting healthy young adults.

    b. Infants and elders.

    c. Overweight middle-aged adults.

    d. Pet owners.

6. The Surviving Sepsis Campaign developed guidelines known as early goal directed therapy (EGDT). Recommendations were classified into three groups. Which one of the following is not one of the groups?:

a. Those directly targeting severe sepsis.

b. Those targeting general care of the critically ill patient with severe sepsis.

c. Those targeting pediatric patients.

d. Those targeting the elderly.

7. Which is correct regarding the relationship between sepsis and systemic inflammatory response syndrome (SIRS)?:

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.

8. Commensal bacteria (normal flora):

a. Rarely cause sepsis.

b. Are notorious for causing sepsis.

c. Rarely infect immunosuppressed patients.

d. Are medically harmless.

9. 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.

10. 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.

11. Protein C, which helps to control coagulation and is unusually low in patients with sepsis, is sometimes knows as C-reactive protein.:

   a. True

   b. False

12. Death from sepsis is generally the result of:

   a. Kidney failure.

   b. Multiple organ failure.

   c. Pneumonia.

   d. Lactic acidemia.

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. Fever is rare in all sepsis patients.

14. The white blood cell count of a septic patient is:

   a. Generally in the normal range.

   b. Always high.

   c. Always low.

   d. Can be either high or low.

15. Septic shock:

   a. Is caused by cardiac dysfunction such as heart failure or myocardial infarction.

   b. Presents with hypotension that cannot be reversed by fluid resuscitation alone.

   c. Typically presents with low blood lactate levels, low blood concentrations of CO_2, and polyuria.

   d. Requires immediate laboratory testing to determine the causative organism.

16. Toxic shock syndrome is:

   a. Severe staphylococcal bacteremia but without shock.

b. Staphylococcal bacteremia typically diagnosed by positive blood cultures.

c. A form of septic shock triggered by bacterial toxins.

d. A rapid-onset sepsis causing severe lung injury, pulmonary edema, and hypoxemia and requiring mechanical ventilation.

17. In general, time zero for treatment is understood to have begun when the patient first complained of feeling ill.:

a. True

b. False

18. The Surviving Sepsis Campaign guidelines recommend "bundles" of measures that must be completed in:

a. Three and six seconds from time zero.

b. Three and six minutes following time zero.

c. Three and six hours from time zero.

d. Three and six shifts following time zero.

19. Initial fluid resuscitation for sepsis:

a. Attempts to improve tissue perfusion with copious intravenous colloids or crystalloids.

b. Provides electrolyte-rich fluid by mouth to counteract severe dehydration.

c. Should be delayed until 6 hours after the administration of antibiotics because it dilutes their concentration in the circulation.

d. Has been superseded by the early administration of corticosteroids.

20. Antibiotics are a key tool in treating sepsis. They should be given:

a. As soon as sepsis is suspected and before any other treatment begins.

b. As soon as a patent airway and appropriate ventilation are ensured.

c. Along with intravenous fluids during the initial resuscitation.

d. As soon as basic patient data are collected and preferably right after blood cultures have been drawn.

21. Empiric antibiotics are:

a. Also known as fourth-generation antibiotics.

b. Given before the microbes causing sepsis have been identified.

c. Coated antibiotic tablets to prevent irritation of the stomach.

d. Administered to SIRS patients as a prophylaxis.

22. Once a septic patient has been started on a particular empiric antibiotic regimen:

a. It is critical to give the full 7 to 10 days of treatment before making any change.

b. New antibiotics should be added if the patient's initial fever persists.

c. New antibiotics should be added if the patient's white blood cell count continues to rise.

d. The need for and the choice of antibiotic should be reassessed daily.

23. In sepsis, "source control" means:

a. Reduction of nosocomial infections.

b. Guarding access to those Schedule II–controlled substances used for patients with sepsis.

c. Removal of the nidus of the infection and of any necrotic tissue.

d. Isolation of patients with sepsis.

24. In septic patients, mechanical ventilation is:

a. Used as a last resort because of the difficulty of weaning patients from dependence on the machine.

b. Needed only when vasopressors are being used to treat hypotension.

c. Commonly needed.

d. Rarely needed.

25. Combating hyperglycemia by limiting blood glucose levels in septic patients to <180 mg/dl:

a. Should be done using insulin.

b. Is critical for diabetic patients but not necessary for non-diabetics.

c. Will worsen survival rates and should be avoided.

d. Should be done by restricting glucose intake.

26. A count of the number of organ failures in a patient with sepsis identifies:

a. The patient's current immune status.

b. Patients who will benefit from a transplant.

c. Those patients with an underlying Gram-negative infection.

d. Patients who have a high risk of dying.

27. Updated recommendations and guidelines for treating sepsis are published in journals and on the Internet by the:

a. International Surviving Sepsis Campaign.

b. FDA.

c. International Savings Program.

d. International Red Cross.

28. Antibiotics should always be delayed until the source of the infection is located for best outcome.:

a. True

b. False

Answer Sheet

Sepsis: Immune Response Meltdown

Name (Please print your name): _____

Date: _____

Passing score is 80%

1. _____
2. _____
3. _____
4. _____
5. _____
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23. _____

24. _____

25. _____

26. _____

27. _____

28. _____

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

* Upon completion of the course, I was able to:

a. Explain the pathophysiology of sepsis.

    ○ 5   ○ 4   ○ 3   ○ 2   ○ 1

b. Define sepsis, severe sepsis, and septic shock.

    ○ 5   ○ 4   ○ 3   ○ 2   ○ 1

c. Identify 3 groups of people with the highest risk of developing sepsis.

    ○ 5   ○ 4   ○ 3   ○ 2   ○ 1

d. Summarize 3 important components of the body's response to infection during a septic reaction.

    ○ 5   ○ 4   ○ 3   ○ 2   ○ 1

e. Name 3 important diagnostic signs and laboratory values of sepsis.

    ○ 5   ○ 4   ○ 3   ○ 2   ○ 1

f. Discuss the clinical presentation of septic shock.

    ○ 5   ○ 4   ○ 3   ○ 2   ○ 1

g. Explain the three-hour and six-hour bundles in the treatment of sepsis.

    ○ 5   ○ 4   ○ 3   ○ 2   ○ 1

h. Name 2 elements of supportive therapy of severe sepsis.

    ○ 5   ○ 4   ○ 3   ○ 2   ○ 1

i. Identify 5 predictive risk factors for increased mortality from sepsis.

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

j. Explain the scoring systems for determining a prognosis in sepsis.

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

k. Discuss prevention approaches to sepsis.

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

l. Explain the patient experience with sepsis and care measures.

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

* The author(s) are knowledgeable about the subject matter.

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

* The authors cited evidence that supported the material presented.

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

* Did the course contain discriminatory or prejudicial language?

○ Yes ○ No

* Was the course was free of commercial bias and product promotion?

○ Yes ○ No

* As a result of what you have learned, do you intend to make any changes in your practice?

○ Yes ○ No

If you answered Yes above, what changes do you intend to make? If you answered No, please explain why.

* Do you intend to return to ATrain for your ongoing CE needs?

○ Yes, within the next 30 days.

○ Yes, during my next renewal cycle.

○ Maybe, not sure.

○ No, I only needed this one course.

* Would you recommend ATrain Education to a friend, co-worker, or colleague?

○ Yes, definitely.

○ Possibly.

○ No, not at this time.

* What is your overall satsfaction with this learning activity?

○ 5　○ 4　○ 3　○ 2　○ 1

* Navigating the ATrain Education website was:

○ Easy.

○ Somewhat easy.

○ Not at all easy.

* How long did it take you to complete this course, posttest, and course evaluation?

○ 60 minutes (or more) per contact hour

○ 50-59 minutes per contact hour

○ 40-49 minutes per contact hour

○ 30-39 minutes per contact hour

○ Less than 30 minutes per contact hour

I heard about ATrain Education from:

○ Government or Department of Health website.

○ State board or professional association.

○ Searching the Internet.

○ A friend.

○ An advertisement.

○ I am a returning customer.

○ My employer.

○ Other

○ Social Media (FB, Twitter, LinkedIn, etc)

Please let us know your age group to help us meet your professional needs.

○ 18 to 30

○ 31 to 45

○ 46+

I completed this course on:

○ My own or a friend's computer.

○ A computer at work.

○ A library computer.

○ A tablet.

○ A cellphone.

○ A paper copy of the course.

Please enter your comments or suggestions here: _____

_____

_____

_____

Registration Form

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

* Name: _____

* Email: _____

* Address: _____

* City: _____ ***** State: _____ ***** Zip:

_____

* Country: _____

* Phone: _____

* Professional Credentials/Designations:

_____

Your name and credentials/designations will appear on your certificate.

* License Number and State: _____

* Please email my certificate:

⊙ Yes   ⊙ No

(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.**
5 contact hours: $29

Credit card information

* Name: _____

Address (if different from above): _____

* City: _____ ***** State: _____ ***** Zip:

_____

* Card type:

⊙ Visa   ⊙ Master Card   ⊙ American Express   ⊙ Discover

* Card number: _____

* CVS#: _____

* Expiration date: _____