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An Overview of Sepsis

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The purpose of this paper was to briefly define sepsis, severe sepsis, and septic shock and discuss evidence-based guidelines for implementing a sepsis protocol in the critical care setting. In addition, this article will further educate critical care nurses about sepsis and strategies to improve outcomes in this group of patients.
Keywords: Sepsis, Sepsis protocol, Septic shock, SIRS

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A critical care nurse is making her assessment rounds during the night shift. When she enters the room of a patient, she does her usual survey for an initial clinical picture. This patient, Ms Wright, a 65-year-old female, appears lethargic. She arrived to the unit as a rapid response patient from the medical-surgical unit. Intravenous fluids are infusing. The monitor shows sinus tachycardia at a rate of 102 beats per minute, a blood pressure of 85/50 mm Hg, and a respiratory rate of 34 breaths per minute. Her rectal temperature is 39°C. A quick look at the urinary catheter drainage bag shows scant drainage. These are all sudden changes in her status. The critical thinking nurse quickly assesses that this patient admitted with pneumonia and respiratory distress may be developing severe sepsis. She notifies the physician. Later that night, the patient is intubated and placed on mechanical ventilation. We, the healthcare staff, have to manage the failing organ systems and clinical manifestations as they occur. This article will explore a more preventive strategy in the treatment of sepsis.

Sepsis is a complex syndrome that occurs as a result of the systemic manifestation of infection.[1] The purpose of this article was to define sepsis, severe sepsis, and septic shock. The critical care nurse's role will be integrated into a discussion of sepsis awareness. In addition, we will discuss the treatment of sepsis, signs and symptoms of sepsis, and strategies to improve the outcome of sepsis and to decrease its mortality. Lastly, the use of a sepsis protocol in relation to critical care is discussed. The use of a sepsis protocol should encourage timely, organized, and aggressive therapy in the treatment of the septic patient.

The Center of Disease Control reports sepsis as the 10th leading cause of death in the United States.[2] Despite advances in the clinical world, sepsis syndrome is still associated with a high mortality rate.[3] The Center of Disease Control released the National Hospital Discharge Survey results, which showed that the rate of hospitalization for septicemia has significantly increased (48%) for those aged 65 years and older.[4] Moreover, the reported rates of severe sepsis average approximately 10 cases per 100 intensive care unit admissions.[3] The mortality rate for inpatients with sepsis is approximately 30% to 55% and increases in the older population.[5]

Sepsis syndrome is still associated with a high mortality rate.

PROGRESSION OF THE DEFINITION OF SEPSIS

The American College of Chest Physicians and the Society of Critical Care Medicine convened in 1991 and introduced into common practice the term *systemic inflammatory response syndrome* or *SIRS*.[6] Thus, sepsis was defined as the presence of infection plus SIRS. The definitions of sepsis, severe sepsis, and septic shock from the conference became widely used in practice.[7] Although somewhat subjective, this classification has been used in epidemiologic studies and clinical trials.

The definition of SIRS, a systemic inflammatory response syndrome to a variety of severe clinical insults, is characterized by 2 or more of the following conditions:

1. temperature higher than 38°C or lower than 36°C,
2. heart rate greater than 90 beats per minute,

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3. respiratory rates greater than 20 breaths per minute or $PaCO_2$ lower than 32 Torr, and
4. white blood cell count higher than 12,000 cells per microliter or lower than 4,000 cells per microliter or the presence of more than 10% immature neutrophils or band cells.

An International Sepsis Definition Conference was held in 2001 to evaluate the strengths and weaknesses of the definition of sepsis and identify methods of improving the definition.[8] The Society of Critical Care Medicine, the European Society of Intensive Care Medicine, the American College of Chest Physicians, the American Thoracic Society, and the Surgical Infection Society were represented at this meeting. These professional groups were responding to medical research, which challenged the definition of sepsis provided in 1992.

The most recent definition of sepsis is largely unchanged. Sepsis is still defined as a clinical syndrome characterized by the presence of both infection and a systemic inflammatory response.[8] However, the criteria defining SIRS have greatly expanded and are separated into 5 categories: (1) general, (2) inflammatory, (3) hemodynamic, (4) organ dysfunction, and (5) tissue perfusion. Parameters such as changes in the patient's temperature, pulse, and mentation are associated with sepsis. Inflammatory variables include changes that would appear in the blood work, such as leukocytosis and increased levels of C-reactive protein. Hemodynamic variables relate to a change in the patient's mean arterial pressure or systolic blood pressure. The next category describes organ dysfunction such as coagulation abnormalities and oliguria. Lastly, tissue perfusion is described as hyperlactatemia.

PATHOPHYSIOLOGY

The pathophysiology of sepsis begins with the entry of organisms into the bloodstream through the skin or the respiratory, genitourinary, or gastrointestinal tract.[9] The entry organism may include bacteria, yeast, viruses, and/or parasites. This complex syndrome is characterized by simultaneous activation of inflammation and coagulation in response to microbial insult.[10] Cytokines are also released, which play a key role during the inflammatory and immune response. Also, cytokines further the cascade of immune response. As the organisms circulate in the bloodstream, more phagocytes, leukocytes, and cytokines are released or activated.[10] The cytokines and white blood cells trigger vasodilation to increase capillary permeability, neutrophil activation, and adhesion of platelets to the endothelium.

Baroreceptors in the carotid arteries and aorta respond to a drop in the patient's blood pressure and activate the sympathetic nervous system.[11] This activation stimulates release of potent vasoconstrictors, epinephrine, and norepinephrine to maintain blood flow to the vital organs: the heart and brain. Simultaneously, blood is shunted from the nonvital organs such as lungs, kidneys, gastrointestinal tract, and skin. For example, decreased blood flow to the kidneys activates the renin-angiotensin-aldosterone system. This process eventually affects cardiac output, circulating volume, and blood pressure. This leads to multiple organ dysfunction syndrome (MODS) and, ultimately, death.[11]

PATIENTS AT HIGHEST RISK

The patient populations most susceptible to sepsis include those with the following characteristics: (1) age younger than 1 year or older than 65 years, (2) chronic illness, (3) immunosuppression, (4) broad-spectrum antibiotic use, and (5) exposure to infection associated with surgical and invasive procedures.[1] Advanced age is related to a decline in immune function.[12] The term used to describe this phenomenon is *immunosenescence*.[13] Studies have indicated that age-related changes in the immune system leads to T cell and B cell impairment among others beyond the scope of this discussion.[14] Physical deficits that contribute to the high risk of sepsis in the elderly include (1) dementia, (2) decreased gag and cough reflex, (3) immobility, (4) skin breakdown, (5) poor urinary bladder emptying, and (6) obstruction leading to infection (urolithiasis, neoplasm, and cholelithiasis).[12]

Patients with community-acquired or nosocomial infections may develop sepsis syndrome. The most commonly community-acquired infection to progress into sepsis is pneumonia.[3] Nosocomial-acquired sepsis is a risk in the critical care setting due to the use of invasive catheters, indwelling urinary catheters, ventilators, and intravascular access. In addition, surgical patients are at risk for nosocomial infection, especially pneumonia.[15] A nosocomial sepsis infection is determined by a positive blood culture taken 48 hours after admission.[16] The most common causative agent for nosocomial agents was *Staphylococcus aureaus*.[17]

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SEVERE SEPSIS

Severe sepsis is defined as sepsis complicated by organ dysfunction.[8] Sepsis may develop into severe sepsis and is associated with organ dysfunction, sepsis-induced hypotension, and hypoperfusion abnormalities such as lactic

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acidosis, oliguria, and acute alteration of mental status.[6] One study reported that severe sepsis occurred in one-half of all hospitalized community-acquired pneumonia patients.[18] In addition, most patients who acquire severe sepsis do so on the first day of hospital admission. Other sources of outpatient infection include urinary tract infections and intra-abdominal infections.[19]

The hypoperfusion of the circulatory system at this stage may lead to organ dysfunction. For example, dysfunction of the pulmonary system may manifest as acute respiratory distress syndrome. Other organ systems may follow, leading to MODS.

SEPTIC SHOCK

Septic shock is the presence of sepsis and a state of acute circulatory failure characterized by refractory arterial hypotension unexplained by other causes.[8] Hypotension is defined as a systolic arterial pressure of less than 90 mm Hg or a reduction of more than 40 mm Hg from baseline despite fluid resuscitation, in the absence of another cause of hypotension. The patient is dependent on vasopressors at this point.[8] The transition from sepsis to septic shock occurs most often during the first 24 hours of hospitalization. Septic shock carries with it an increase not only in morbidity but also in mortality.[20]

SEPSIS DIAGNOSIS AND DIAGNOSTIC TESTING

The diagnosis of sepsis is difficult, especially in the critical care setting, wherein early signs and symptoms are often superimposed by the patient's underlying illness. Early organ dysfunction may be the first symptom noted by clinicians.[8] Other diagnostic criteria may include (1) hemodynamic instability, (2) arterial hypoxemia, (3) oliguria (less than 0.5 mL/kg/h), (4) coagulopathy, and (5) altered liver function tests. The list of criteria was set by the International Sepsis Definitions Conference.

Serum lactate level is a diagnostic marker in septic patients.[8] Lactate is generated by anaerobic cellular metabolism and may reflect the degree of cellular derangements in sepsis. Arterial lactate levels are commonly used as a global indicator of oxygen deficits. Serial lactate levels can reflect adequacy of hemodynamic resuscitation efforts.

Multiple serological markers may aid in the early diagnosis of sepsis. Because of the complexity of the sepsis syndrome, numerous studies have been conducted to identify laboratory tests that may shorten the time to diagnosis sepsis. For example, much research has been conducted to study procalcitonin (PCT), which is a propeptide of calcitonin.[21] In patients with sepsis, PCT levels may increase up to 5,000 to 10,000 times the normal range. Elevated PCT levels in patients with severe sepsis and septic shock have been noted.[22]

A recent study focused on the measurement of specific cytokine levels such as plasma tumor necrosis factor, interleukin-6, and interleukin-10.[10] This study included 1,886 participants from 28 hospitals in the United States. High levels of the proinflammatory interleukin-6 and anti-inflammatory interleukin-10 cytokine were associated with a higher risk of death.

Genetic factors are also a focus of studies in relation to why some patients succumb to severe sepsis and septic shock faster than others do.[21] Studies have been conducted to ascertain why patients with similar characteristics (such as age and gender), when exposed to the same pathogen, have different reactions. For example, some patients have been identified with a specific genotype related to a reduction in fibrinolysis.[23] This reduction in fibrinolysis leads to altered clotting pathways, which, in turn, places these patients at a higher risk for MODS or septic shock.

TREATMENT OF SEPSIS

The treatment of sepsis is often focused on supporting failing organ systems with interventions including (1) fluid replacement, (2) airway management, (3) antibiotic therapy, and (4) use of vasopressors. The goals of fluid resuscitation in septic shock are restoration of tissue perfusion and normalization of oxidative metabolism.[24] Increasing cardiac output and oxygen delivery is dependent on expansion of blood and plasma volume.[25] Invasive hemodynamic monitoring via a pulmonary artery catheter should be used in patients who do not respond rapidly to initial fluid boluses or those with poor physiologic reserve.[11] Filling pressures should be increased to a level associated with maximal increases in cardiac output. In most patients with septic shock, cardiac output will be optimized at pulmonary artery occlusion pressures between 12 and 15 mm Hg.[25] Increases above this range usually do not significantly enhance end-diastolic volume or stroke volume and increase the risk of pulmonary edema. If only central venous pressure is available, levels of 8 to 12 mm Hg should be targeted.[11]

Vasopressor therapy should begin when fluid administration fails to restore an adequate arterial pressure and organ perfusion.[26] Vasopressor therapy may also be required transiently to maintain perfusion in the face of life-threatening hypotension, even when adequate cardiac filling pressures have not yet been attained. Potential agents include dopamine, norepinephrine, phenylephrine, epinephrine, and vasopressin.[26]

Antimicrobial therapy should be initiated as soon as blood cultures are taken and other relevant sites have

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been cultured. The choice of initial therapy is based on knowledge of the likely pathogens at specific sites of local infection.[27] Empirical antibiotics that are effective against both Gram-positive and Gram-negative bacteria and should be administered intravenously. Once the organism is identified, then the antibiotic regimen may be simplified.[27]

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Ventilator therapy is indicated for patients with progressive hypoxemia, hypercapnia, neurologic deterioration, or respiratory muscle failure. In addition, mechanical ventilation is often initiated to ensure adequate oxygenation, divert blood from the muscles of respiration, prevent aspiration, and reduce cardiac afterload. Low tidal volumes (6 mL/kg) are recommended to prevent the risk of acute respiratory distress syndrome.[18,28]

Other important treatment modalities for sepsis include (1) tight glycemic control, (2) nutritional support, and (3) corticosteroid administration.[26] Hemoglobin and hematocrit must be monitored, as well as the need for transfusion of blood products. In addition, drotrecogin alfa (activated), or recombinant human activated protein C, has been approved by the Food and Drug Administration for the treatment of severe sepsis.[29] This drug has antithrombotic, anti-inflammatory, and profibrinolytic properties.[30] Activated protein C has been associated with a reduction in the relative risk of death by 19% and an absolute reduction in the risk of death by 6.1%.[29] However, the drug also carries a high risk of bleeding. Nurses should assess for bleeding by monitoring serial hematocrits and activated partial thrombin time. In addition, the nurse should assess bodily secretions for occult and frank bleeding.[30]

SEPSIS PROTOCOL

Advances in the management of sepsis have occurred over the past decade. However, despite improved interventions, severe sepsis and septic shock continue to be associated with high mortality and morbidity.[3] Research suggests a multifaceted, aggressive protocol approach toward the treatment of sepsis.[24]

Multiple studies have been performed using similar versions of a sepsis protocol or "bundle of treatments" in search of methods to recognize sepsis early and effectively treat this complex illness.[31] For example, a retrospective analysis study that used an organized hospitalwide sepsis protocol system found decreased mortality rates and costs. Early goal-directed therapy is a sepsis cardiovascular support protocol aimed at early hemodynamic optimization within the first 6 hours of recognition of sepsis.[20] These first 6 hours are considered critical to therapy response.[32] Early goal-directed therapy includes (1) intravenous fluids, (2) vasopressors, (3) packed red blood cells, (4) timely administration of antibiotics, (5) low-dose steroids for adrenal insufficiency, (6) activated protein C, and (7) prophylaxis against deep venous thrombosis and stress ulcers.[31]

EXAMPLES OF QUALITY INDICATORS IN A SEPSIS PROTOCOL

Research suggests initiation of the protocol in 2 steps. First, initiation of treatment measures should begin in the emergency department and second, maintenance therapy. Initial measures include the following:[33]

1. obtain blood cultures before antibiotic administration,
2. have an early initiation of antibiotics,
3. measure serum lactate level,
4. maintain adequate central venous pressure (greater than 8 mm Hg),
5. maintain adequate central venous oxygen saturation (greater than 70%),
6. treat hypotension and/or elevated lactate (greater than 1.5 times the upper limit of normal) with fluids, and
7. use of vasopressors for ongoing hypotension.

Maintenance therapy includes the following:

1. low-dose steroids administered for septic shock in accordance with a standardized critical care policy,
2. drotrecogin alfa (activated) administered in accordance with a standardized policy,
3. glucose control maintained at the lower limit of normal but less than 150 mg/dL (8.3 mmol/L), and
4. inspiratory plateau pressures maintained less than 30 cm H_2O for mechanically ventilated patients.[26]

INITIATION OF THE SEPSIS PROTOCOL AND CHALLENGES OF THE PROCESS

Despite data supporting improved outcomes with protocol-based algorithms, their application has still not become routine in hospitals.[32] One large hospital demonstrated the successful initiation of a multidisciplinary sepsis protocol.[33,34] One of the challenges in the protocol initiation was the timely placement of a central venous oxygen saturation catheter. However, another study used the same protocol except for the oxygen saturation monitoring and found the same positive results.[24]

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A number of processes may be initiated to ensure successful adoption of the guidelines.[1] For example, guidelines for improving care for patients with severe sepsis or septic shock may be discussed during daily rounds, grand rounds, and critical care conferences. A customized hospital protocol could be developed with standardized order sets for septic patients to promote uniformity of care.[35] Research has demonstrated that the implementation of a standardized order set for the management of septic shock in the emergency department is associated with statistically more rigorous fluid resuscitation in patients, administration of appropriate initial antibiotic treatment, and lower 28-day mortality.[35]

THE ROLE OF THE CRITICAL CARE NURSE

The purpose of the Surviving Sepsis Campaign (developed by the European Society of Intensive Care Medicine, the Society of Critical Care Medicine, and the International Sepsis Forum) is to create an international collaborative effort to improve the treatment of sepsis and reduce the mortality rate associated with this condition.[26] See Table 1.

The key is early recognition of signs and symptoms of sepsis before extreme measures such as mechanical ventilation are needed. Collaborative efforts can reduce the mortality of patients and decrease costs. Nurses throughout the hospital may become involved by starting a surviving sepsis campaign to raise awareness and promote education. Rapid response calls may often be for patients in severe sepsis or septic shock.

CONCLUSION

In continuation, during the course of Ms Wright's stay in the intensive care unit, she received activated protein C, vasopressors, packed red blood cell transfusions, and aggressive fluid therapy. In addition, tight glycemic control was maintained. The patient was extubated on day 6 and was transferred to the medical unit on day 8. Ms Wright recovered successfully.

Severe sepsis and septic shock are life-threatening conditions that pose high morbidity and mortality rates for critically ill patients. Moreover, the complexity of this syndrome is still not fully understood and requires continuous research. The treatment of sepsis is time-sensitive, which may be improved through the use of a sepsis protocol. Current research on the initiation of measures designed for early recognition and treatment of sepsis have shown improved outcomes. These interventions with education about the risk factors, manifestations of the illness, and pathophysiology may promote better patient care in the critical care setting. The critical care nurse plays a leading role in early detection, monitoring, and treatment of patients with these conditions. Thus, with education, use of protocols and healthcare professionals working together should positively impact critically ill septic patients.

TABLE 1 Internet Sources of Information Concerning Sepsis

American Sepsis Alliance: www.sepsisalliance.org
Institute for Health Improvement: www.jhi.org
International Sepsis Forum: www.sepsisforum.org
Society of Critical Care Medicine: www.sccm.org

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