11 Septic shock

Bryan E. Freeman and Michael R. Foley

INTRODUCTION/EPIDEMIOLOGY

The idea that infectious etiologies underlie many complications related to illness and medical and surgical procedures is a relatively young area of interest and understanding in the medical profession. Throughout time, scientists have considered that toxins, miasmas, and “bad humors” may be the culprits behind various disease processes, but it was not until the last 300 years that a viable link between bacteria and infection, including sepsis, has been made.

Sir John Pringle’s work in the 1700s relating the ideas of septic and antiseptic conditions to systemic diseases such as fever and dysentery in jails and on the battlefield as relating was a step in the right direction, despite an incorrect mechanism of infection. Although he blamed “putrid air” as the source of disease, awareness of his ideas led to a decrease in the incidence of sepsis (1).

Further advances in medical understanding of the etiology behind infectious diseases were made in the 1800s. The French chemist, Louis Pasteur, discovered that microorganisms were responsible for disease, and Joseph Lister, the English surgeon, was responsible for the introduction of sterilization of surgical instruments and sterile technique. The 1900s brought Alexander Fleming’s discovery of penicillin to combat gram-positive bacteria.

Shock, also known as physiologic or circulatory shock, is an alteration in normal physiology that results in severe and potentially life-threatening changes in the circulatory system. There are various categories of shock, but the most common are cardiogenic, hypovolemic (hemorrhagic), and septic shock. While the etiologies behind these categories are different, the effect on the body is essentially the same. The result of shock is a cascade of events that includes hypoperfusion of tissues, cellular hypoxia, metabolic acidosis, and eventually cellular death.

The incidence of sepsis is difficult to determine due to a lack of use of appropriate terminology as well as inaccurate reporting. However, recent data in the United States regarding severe sepsis have shown an overall rate of three cases per 1000 population, with a substantial, directly proportional increase with increasing age. Outcomes are variable based upon the etiology and underlying comorbidities of the individual, as well as by location of infection. Annual national costs relating to sepsis are estimated to be \$16.7 billion per year in the United States alone (2).

Sepsis remains one of the most significant causes for medical morbidity and mortality worldwide. It was responsible for 9.3% of all deaths in the United States in 1995 and has been shown to have a 30% mortality rate, although this varies depending upon the patient population (2).

Septic shock affects an estimated one in 8338 deliveries (3). However, much of the data relating to sepsis and septic shock

deals with a non-obstetric population. Generally, since women of childbearing age are young, healthy women, without the serious comorbidities of the elderly populations that are usually studied, rates are significantly lower. In fact, a review of the percentage of total cases of sepsis in the United States demonstrated that pregnant patients comprised approximately 0.6% of all cases in 1979 to 1984, but 0.3% of cases in 1995 to 2000 (4).

Despite the fact that sepsis is such a concern worldwide, a surprising number of people have not heard of, much less understand, what sepsis is. A study performed using telephone interviews of 6021 citizens in Italy, Spain, the United Kingdom, France, and the United States revealed that public knowledge of simply the term “sepsis” was astonishingly low and that 58% of those surveyed did not know that sepsis is a leading cause of death (5). The implications of this alone may indicate why early sepsis and its significance may present challenges in the treatment of less severe disease.

ETIOLOGY

Causes of bacteremia in the obstetric population may be due to a single or multiple pathogens and may be made in patients with different illnesses. Blanco et al. found that the most common pathogens were *Escherichia coli* (32%), group B streptococcus (16%), and *Bacteriodes* spp. (15%), each of which led their respective categories of gram-negative, gram-positive, and anaerobic bacteria, respectively (6). The conditions that these infections were associated with were variable, but have been shown to be the most prominent etiologies in other studies. Of 176 patient studies, diagnoses included endometritis (70%), pyelonephritis (16%), chorioamnionitis (8%), and various other causes (6). Therefore, sepsis in the obstetric population is a concern both antepartum as well as postpartum.

Septic shock has been shown to be associated with the same conditions, but in a slightly different order of frequency according to recent studies. Mabie et al. in 1997 published an article that examined the outcomes of 18 women with septic shock in pregnancy. Their definition of septic shock conforms to the definition set forth by the 1992 American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference (7). The mortality rate was 28%, with etiologies for septic shock ranging from pyelonephritis (33%), chorioamnionitis (17%), toxic shock (11%), and postpartum endometritis (11%). The remaining causes included septic abortion, ruptured appendix, ruptured ovarian abscess, necrotizing fasciitis, and bacterial endocarditis (approximately 5% each). Etiology varied due to the clinical history of the patient and the presence of significant comorbidities. Other significant findings were that depressed left ventricular function was noted in 64% of survivors and

80% of those that died. Organisms isolated from cultures included *Escherichia coli*, group A streptococcus, group B streptococcus, *Klebsiella pneumoniae*, *Streptococcus viridans*, *Staphylococcus epidermidis*, and others. Of note, *E. coli* was present in 61% of patients, and there was one patient who was culture negative (3).

PATHOPHYSIOLOGY

Despite the continual discovery of new cytokines, intercellular relationships, and systemic changes that accompany the sepsis spectrum of diseases, the precise mechanisms behind severe sepsis and septic shock are not completely understood. Under normal conditions, the site of bacterial infection is targeted by the body's natural immune response. This involves an increase in inflammatory cytokines, activation of the clotting cascade, and decreased fibrinolysis in a localized fashion. In the setting of a normally functioning immune system, this leads to the body being able to effectively eliminate the invading pathogen, after which damage caused by the insult may be repaired.

Sepsis and septic shock, on the other hand, are exaggerations of the body's natural response to infection. Pro-inflammatory and anti-inflammatory mediators are upregulated, along with the natural immune response, but on a systemic scale, with effects far beyond the area in which it is needed. The precise mechanisms behind the regulation of a normal immune response and the lack of regulation in sepsis-related conditions are an area of ongoing research and interest. Understanding of the signaling pathways and resultant mediators produced has advanced greatly over recent years.

An extensive summary of current knowledge about the molecular biology behind inflammation and sepsis was published by Cinel and Opal in early 2009. The following are selections from this article that shed light on the mechanisms involved in these processes (8).

One popular area of sepsis research is the examination and elucidation of mechanisms behind the action of toll-like receptors (TLRs). Essentially, TLRs function to activate immune responses once the body's natural barriers (skin, vascular system, etc.) have been breached. Current research has shown that binding of TLRs causes activation of intracellular transcription activators including interferon regulator factors, phosphoinositide 3-kinase (PI3K), and cytosolic nuclear factor-kappa β (NF- β). NF- β then enters the nucleus and ultimately causes the activation of genes for acute phase proteins, inducible nitric oxide synthase, coagulation factors, and pro-inflammatory cytokines, among others (8).

The significance of PI3K is that it can either positively or negatively regulate TLRs in order to influence pro-inflammatory cytokine production. For instance, positive regulation of TLRs by PI3K leads to increased production of pro-inflammatory cytokines interleukin-1 β (IL-1 β), IL-6, and IL-8 (8).

Sepsis also leads to increased neutrophil activation. Normally, these proapoptotic neutrophils are responsible for the effective clearance of the invading pathogen while remaining well controlled so as not to damage healthy host cells. In sepsis, neutrophils have been found to evade the normal clearance by macrophages, which usually regulate their number and effect. This lack of regulation leads to increased

numbers of circulating neutrophils, which have a pro-inflammatory effect (8).

Along these same lines, macrophage migration inhibitory factor (MIF) is induced by glucocorticoids in sepsis and is probably involved in sepsis pathogenesis. Experiments in mice have found that inhibition of MIF leads to attenuation of inflammatory mediators such as TNF- α and IL-1 β (8).

Tumor necrosis factor α (TNF- α or cachectin), which is produced primarily by macrophages, and secondarily released from damaged endothelial cells, is a pro-inflammatory cytokine. It acts with other cytokines, such as IL-1 and IL-6, to cause various alterations in the function of multiple organs. In the setting of sepsis, insulin resistance and fever increased.

Activation of the clotting cascade is another mechanism by which the body fights infection and its effects. The formation of a clot (which serves as an intravascular barrier) and initiation of inflammation are attempts to isolate the area of infection and prevent systemic spread of the pathogen. However, this is not always held in check, resulting in sepsis and related conditions. In sepsis, the extrinsic (tissue factor) pathway is activated, leading to increased thrombin production. This is the target of action of activated protein C, which will be discussed later (8).

DIAGNOSIS

Initial diagnosis of septic shock and related conditions include a thorough history and physical examination, baseline laboratory tests, and blood cultures. The history can help to elucidate the etiology of the septic shock and to direct treatment. This is important as a simple clinical history can help elucidate a probable etiology for the condition.

In general, baseline laboratory tests that need to be obtained include a complete blood count, at least two blood cultures, coagulation studies, a complete metabolic panel, and any other cultures that are deemed clinically applicable. Specific recommendations are outlined in the following paragraphs.

In order to properly diagnose which entity is involved, understanding of the currently accepted definitions is essential. The terminology surrounding the sepsis spectrum of disorders has been inconsistently and incorrectly utilized, leading to misunderstanding of the disease process involved. This has led to a variety of terms being used for a spectrum of conditions related to sepsis such as bacteremia and septicemia. Other etiologies for conditions resembling sepsis exist, and it has not been until the past two decades that an attempt has been made to clarify the differences between these entities.

Therefore, it is more appropriate to think of sepsis and related conditions as a continuum of conditions that overlap to various degrees. They share the same etiologies, but have more serious implications the further they exist along this continuum.

In recognition of this, the ACCP/SCCM has established more firm definitions. In 1992, the members of the ACCP/SCCM Consensus Conference made four recommendations to create more precise terminology for sepsis-related entities. Along with this, they introduced the term "systemic inflammatory response syndrome" (SIRS). The goal of these formal definitions was to give clinicians the ability to

differentiate between illnesses in order to better direct patient care. The disease categories now include sepsis, severe sepsis, SIRS, septic shock, sepsis-induced hypotension, and multiple organ dysfunction syndrome (7).

SIRS can be the result of a variety of injuries (trauma, infection, burns, or sterile inflammatory processes such as pancreatitis) that lead to a series of complex findings. Assigning the diagnosis by 1992 criteria initially required at least two of the following:

1. Body temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$
2. HR >90 bpm
3. Tachypnea (RR $>20/\text{min}$) or hyperventilation ($\text{PaCO}_2 <32$ mmHg)
4. WBC count $>12,000$ cells/ μL or <4000 cells/ μL , or presence of bands (7)

Sepsis is the systemic inflammatory response that is due to an infection. More simply, it is SIRS that has occurred due to an infectious process. The clinical and laboratory criteria are therefore the same as listed for SIRS (7). This allows a differentiation to be made between the other potential etiologies that may lead to SIRS and clearly identifies a specific subdivision of SIRS.

In order to clarify other terms that are commonly used with sepsis, they proposed the following definitions. Infection is the invasion of a normally sterile host by an organism that leads to an inflammatory response. Bacteremia refers to viable bacteria in the blood. If the invading pathogen is not bacteria, the appropriate corresponding term should be employed (viremia, fungemia, etc.) (7).

Severe sepsis is sepsis complicated by organ dysfunction, hypoperfusion abnormality (lactic acidosis, oliguria, or altered mental status), or sepsis-induced hypotension (7). Sepsis-induced hypotension is systolic blood pressure <90 mmHg or a decrease in systolic blood pressure of ≥ 40 mmHg from baseline, without any other identifiable cause for hypotension (7).

Septic shock is a subdivision of severe sepsis and is defined as sepsis-induced hypotension (as defined above) that is unresponsive to fluid resuscitation, accompanied by hypoperfusion abnormalities or organ dysfunction. This definition still applies to patients who have been treated with vasopressors, as hypoperfusion abnormalities and organ dysfunction may not occur until after treatment (7).

Septicemia has been determined to be an inaccurate term, and the members of the ACCP/SCCM Consensus Conference have recommended its removal from sepsis vocabulary (7).

The definitions set forth at the 1992 ACCP/SCCM Consensus Conference were reevaluated after almost a decade of use. Representatives from Europe and the United States met at the 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference to discuss the efficacy and potential need for modification of the previously mentioned definitions.

Regarding the definition of SIRS, the committee felt that since the clinical signs of inflammation may be quite variable, a specific definition for SIRS was too difficult to formulate. The definition established by conference in 1992 remained unchanged, but with the acknowledgement that it is "overly sensitive and nonspecific" (9). Subcommittees had been

assigned to look at common markers found in sepsis, as well as other laboratory derangements brought about by this condition. Increased levels of IL-6, adrenomedullin, soluble CD14, soluble endothelial cell/leukocyte adhesion molecule 1, macrophage inflammatory protein 1α , extracellular phospholipase A_2 , procalcitonin, and C-reactive protein had been noted by committee members. Although these and other markers may be elevated during times of inflammation, there are no laboratory panels to create from these to function as a diagnostic tool for SIRS. However, understanding of the significance of the individual markers may aid in targeting specific treatment to a given organ, the coagulation cascade, and so on (9).

The definition of septic shock was expanded minimally to include a mean arterial pressure (MAP) <60 . The definitions for infection, sepsis, and severe sepsis remained essentially unchanged (9).

Aside from the reevaluation of definitions for the spectrum of sepsis conditions, the 2001 Committee developed a prototype classification tool for sepsis, called PIRO. This mnemonic represents

1. predisposing conditions,
2. insult (the nature and extent of the insult),
3. response (the nature and magnitude of the host response), and
4. organ (the degree of organ dysfunction).

Based upon the utility derived from this in subsequent studies, this tool may be of use in the future for assigning a prognosis or determining the appropriate treatment protocol for patients with sepsis (9).

Although pregnant women were excluded from the study, a group of researchers recently explored the possibility of utilizing a biomarker panel to predict serious outcomes for patients with suspected sepsis who were admitted through the emergency department. The primary outcome was to predict the probability of development of sepsis and the secondary outcomes included septic shock and inpatient mortality. Nine biomarkers were studied in all, but the combination of protein C, IL-1 receptor antagonist (IL-1ra), and neutrophil gelatinase-associated lipocalin (NGAL) was found to be the most predictive of identifying both primary and secondary outcomes. Protein C is a marker of activation of coagulation, IL-1ra indicates inflammation, and NGAL reflects renal dysfunction. This may be an area of future research to help direct physician intervention at the time of initial assessment. The results of these tests were used by the authors to arrive at a Sepsis Score (10). When this has undergone further testing, there may be utility for treating the obstetric population as well.

MANAGEMENT

Management recommendations are largely based upon work that has been done in the non-obstetric population. Therefore, there are not established protocols to deal with the pregnant patient with septic shock or that take into account the significant physiologic changes that accompany pregnancy and how these changes may alter the effectiveness of a given therapy. The basic goals of therapy, which have been used successfully, are based upon early detection and diagnosis of

the problem, aggressive fluid resuscitation and use of vasopressors, glycemic control, corticosteroids, and, more recently, the utilization of activated protein C (11).

Expanding upon this, in 2008, the Surviving Sepsis Campaign Committee published updated guidelines for the management of severe sepsis and shock. Extensive evaluation of each step of severe sepsis management was performed, and a grading system was then used to assign which interventions were either recommended or simply suggested, according to the strength of supporting evidence. Initial management was divided into 10 categories: initial resuscitation, diagnosis, antibiotic therapy, source control, fluid therapy, vasopressors, inotropic therapy, corticosteroids, activated protein C, and use of blood products, which are summarized below (12).

The Surviving Sepsis Campaign protocol for initial resuscitation should be initiated as soon as tissue hypoperfusion (persistent hypotension despite fluid administration or serum lactate concentration ≥ 4 mmol/L) is recognized. The goals during the first 6 hours of therapy are as follows:

1. Central venous pressure = 8 – 12 mmHg
2. MAP ≥ 65 mmHg
3. Urine output ≥ 0.5 mL/kg/hr
4. Central venous oxygen saturation $\geq 70\%$ or mixed venous oxygen saturation $\geq 65\%$

If these criteria are not able to be met within 6 hours, the committee suggests transfusing packed red blood cells until a hematocrit is $\geq 30\%$ is reached and/or administering dobutamine up to 20 $\mu\text{g/kg/min}$ (12).

Diagnostic studies should be performed quickly. If possible, prior to the administration of antibiotics, at least two blood cultures should be obtained, in addition to cultures of intravascular devices (and each lumen of these devices) greater than 48 hours old. Other areas representing potential sources of infection, such as urine, wounds, respiratory tract, and so on, should be cultured according to clinical suspicion. If, and only if, obtaining any of these cultures risks serious delay of initiation of antibiotic administration, antibiotics should be started first. The cultures must be collected soon thereafter to avoid the risk of sterilization of blood cultures, which may occur within a few hours of antibiotic administration. Additionally, imaging studies should be performed as soon as possible to help confirm a diagnosis (12).

Antibiotic therapy should be initiated as soon as possible with intravenous medications within the first hour of recognition of severe sepsis and septic shock. As previously stated, collection of cultures should ideally be performed prior to antibiotic administration, if possible. Since etiologies of sepsis and septic shock vary depending upon each patient's clinical history and underlying conditions, the choices of antibiotic are also variable and will be dictated by these factors. Recently used antibiotics should be avoided and the choice of a broad-spectrum antibiotic that would cover pathogens associated with the presumed source of infection should be chosen. Other considerations include awareness of the increasing prevalence of methicillin- and oxacillin-resistant *Staphylococcus aureus* (MRSA and ORSA) or whether candidemia is suspected, which would require appropriate antifungal coverage (12).

Additionally, loading doses of antibiotics should be used, but with the awareness of organ damage and large changes in

volume due to fluid resuscitation that may alter serum levels of any medication. Therefore, physicians and pharmacists need to carefully monitor serum levels to avoid toxicity. The recommended course of antibiotics should be at least 7 to 10 days and needs to be tailored to reflect the culture and sensitivity results (12).

Source control needs to be achieved within 6 hours of treatment. This includes establishing a diagnosis, locating the etiology of the infection, and taking steps to appropriately deal with the cause. In the case of an intravascular device being the culprit, it should be removed immediately after alternate intravascular access has been achieved (12).

Fluid therapy should include administration of either colloids or crystalloids. The SAFE study demonstrated no difference in efficacy between these two types (13). Goals of fluid resuscitation are initially to achieve a central venous pressure of ≥ 8 mmHg (or 12 mmHg if the patient is mechanically ventilated). Fluid challenges should be administered in the form of either at least 1000 mL of crystalloids or 300 to 500 mL of colloids over 30 minutes. As long as the patient responds to fluid challenges, they should continue. However, if central venous pressures or pulmonary artery pressures increase without simultaneous hemodynamic improvement, the rate of fluid administration should be substantially reduced (12).

Vasopressors should be utilized to maintain MAPs of at least 65 mmHg. The committee recommends that first-line vasopressor therapy should include norepinephrine or dopamine administered via a central line. Epinephrine, phenylephrine, and vasopressin should not be used as first-line therapy, although epinephrine may be used if initial efforts with norepinephrine or dopamine were unsuccessful in achieving the desired MAP. Additionally, low-dose dopamine for renal protection is not recommended (12).

Inotropic therapy with dobutamine may be utilized in patients with evidence of myocardial dysfunction (high cardiac filling pressures and low cardiac output).

Recommendations relating to the utility of corticosteroid treatment in septic shock are largely based upon results from the Corticosteroid Therapy of Septic Shock Study Group. Routine use of corticoid therapy as adjuvant treatment should not be employed in patients with septic shock. The ACTH test is not recommended to determine which patients should receive hydrocortisone treatment. Corticosteroid treatment should be reserved for patients with septic shock only if their hypotension is non-responsive to fluid therapy and vasopressors (12,14). Additionally, since etomidate is frequently used for sedation in the intensive care unit, including care for patients with severe sepsis, care should be taken to avoid performing an ACTH test for any reason in patients who have received etomidate, as it can adversely impact their survival (15).

Activated protein C therapy [also known as recombinant human activated protein C (rhAPC), drotrecogin alfa] should be based upon the diagnosis of the patient and their Acute Physiology and Chronic Health Evaluation (APACHE) II score. The APACHE II score is a tool used to assess the severity of disease in adults admitted to intensive care units and is based upon physical assessment of patients during the first 24 hours of their admission. Patients with severe sepsis, an

APACHE II score >25 or multiple organ failure, and who are deemed to be at high risk of death should receive rhAPC, assuming that they have no contraindications. On the other hand, patients with severe sepsis, an APACHE II score <20 or single organ failure, and who are at low risk for death should not receive rhAPC therapy (12). These recommendations are consistent with conclusions from the Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) Study Group, published in 2005 (16).

Although the exact mechanism is unknown, activated protein C possesses both anti-thrombotic and anti-inflammatory properties. As mentioned before, sepsis involves activation of the extrinsic (tissue factor) pathway of the clotting cascade, which leads to overproduction of thrombin. This is the target of APC. Normally protein C, the zymogen of APC, is activated by thrombin. However, there are two aspects of sepsis that cause disruptions in this system. The first problem is that circulating levels of protein C, APC, and protein S (the cofactor for protein C) are decreased. The other issue is that the thrombin:thrombomodulin complex that is usually responsible for the conversion of protein C to APC is also disrupted, which leads to the unregulated production of thrombin. Administration of rhAPC compensates for the lack of naturally created APC and exerts an anti-thrombotic effect by blocking the conversion of factors VIIIa and Va to factors VIII and V, as well as by inhibiting plasminogen activator inhibitor-1 (PAI-1), thereby allowing fibrinolysis to occur. Other mechanisms may be involved as well (17).

After resolution of hypoperfusion, and in the absence of complicating factors such as myocardial infarction, acute hemorrhage, and so on, administration of blood products (not covered in recommendations for initial resuscitation) may be considered. Packed red blood cells should be transfused for hemoglobin levels <7.0 g/dL, with a target hemoglobin of 7.0 to 9.0 g/dL. The use of erythropoietin is not recommended in the treatment of severe sepsis unless there is another reason for its administration, such as renal failure (12).

Other blood products, such as fresh frozen plasma, may be utilized to correct coagulopathy. Platelet administration should be performed in severe sepsis when platelet counts are <5000/mm³, whether or not the patient is bleeding. For platelet counts in the range of 5000 to 30,000/mm³, platelet transfusion should be considered. Goals of platelet therapy are dependent upon future interventions that are to be made. In the event of anticipated surgery, platelet transfusion should be performed to reach a count of >50,000/mm³ (12).

One final area of management that has received recent attention is that of glucose control in patients with severe sepsis and septic shock. The Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) is the most recent study to address this issue and their findings coincide with prior studies. The investigators randomized patients into groups of either conventional or intensive insulin therapy. The conventional insulin group was treated via insulin drip if blood glucose levels exceeded 200 mg/dL and were maintained in the range of 180 to 200 mg/dL. The intensive insulin therapy group received insulin via insulin drip once blood glucose levels exceeded 110 mg/dL and were maintained in the range of 80 to 110 mg/dL. No benefit was found to intensive insulin therapy. In fact, this treatment was

terminated early by the data and safety monitoring board at the time of the first safety analysis due to the high incidence of hypoglycemia (18).

The Surviving Sepsis Campaign Committee recommends that following patient stabilization, insulin therapy should be initiated. The goal is to maintain blood glucose levels <150 mg/dL, with levels checked every 1 to 2 hours until stable, then every 4 hours (12).

CONCLUSIONS

Fortunately, sepsis and septic shock in pregnancy is a rare entity. Normal pregnancy involves many physiologic changes that would present problems for any other patient due to the increased demands on the cardiovascular and other systems. As noted, the work and recommendations that currently exist for the treatment of the continuum of sepsis conditions are for non-obstetric populations and do not take into account the changes associated with pregnancy. Given the paucity of data that exist strictly in regard to septic shock in pregnancy, it is reasonable to proceed with septic shock management according to these guidelines. Definitions that specify the exact entity within the spectrum of sepsis-related diseases can help focus management and facilitate communication with colleagues. Until specific studies in the pregnant prove otherwise, quick assessment and diagnosis of this condition followed by critical care and emergency protocols should be followed.

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