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# Sepsis in Pregnancy

## *Identification and Management*

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**ABSTRACT**

Sepsis accounts for up to 28% of all maternal deaths. Prompt, appropriate treatment improves maternal and fetal morbidity and mortality. To date, there are no validated tools for identification of sepsis in pregnant women, and tools used in the general population tend to overestimate mortality. Once identified, management of pregnancy-associated sepsis is goal-directed, but because of the lack of studies of sepsis management in pregnancy, it must be assumed that modifications need to be made on the basis of the physiologic changes of pregnancy. Key to management is early fluid resuscitation and early initiation of appropriate antimicrobial therapy directed toward the likely source of infection or, if the source is unknown, empiric broad-spectrum therapy. Efforts directed at identifying the source of infection and appropriate source control measures are critical. Development of an illness severity scoring system and treatment algorithms validated in pregnant women needs to be a research priority.

**Key Words:** antimicrobial agents, early goal-directed therapy, pregnancy, sepsis

Severe sepsis is the leading cause of death in critically ill adults in noncoronary intensive care units (ICUs) in the United States, with a mortality rate of up to 50% of those admitted with septic shock.[1–5] It is the 10th leading cause of death for women and 11th leading cause of death overall.[6] Maternal sepsis, especially puerperal sepsis, is a common pregnancy-related condition and in the United States is a leading cause of maternal mortality, accounting for up to 28% of maternal deaths and up to 15% of maternal admissions to the ICU.[7–11] More concerning is that sepsis has been increasingly reported as the cause of maternal death, rising by 9.1% per year from 2001 to 2010, becoming the most common cause of maternal death in Texas.[10] This is likely related to an over 200% increase in the incidence of pregnancy-associated severe sepsis over that same time period.[12] Similarly, an evaluation of the Nationwide Inpatient Sample between 1998 and 2008 demonstrated a 10% per year increase in maternal severe sepsis and sepsis-related death in the United States.[13]

Overall, maternal morbidity and mortality appear to be on the rise in the United States.[14–16] Because of this, maternal mortality has become a focus in the field of maternal-fetal medicine.[17] A consensus document recently published by representatives of the American Board of Obstetrician Gynecologists, The American Congress of Obstetricians and Gynecologists, the Society for Maternal-Fetal Medicine, and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, while not addressing maternal sepsis specifically, highlights the importance of research focused on the care of medically ill pregnant women.[18]

The purpose of this article, therefore, is to review the common causes of sepsis in pregnancy and provide a framework for the identification of sepsis in pregnancy and the management of both mother and fetus.

## THE SYSTEMIC INFLAMMATORY RESPONSE SYNDROME AND SEPSIS

In 1992, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine

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(SCCM) introduced definitions for the systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock.[19] The idea behind SIRS was to describe a clinical response to a nonspecific insult of either infectious or noninfectious origin.[20] In 2001, an international group of critical care specialists met to solidify these definitions.[19,21] Tables 1 and 2 list the definition and diagnostic criteria for SIRS, sepsis, severe sepsis, and septic shock as defined by this panel. In Table 2, additional factors that are altered by pregnancy are noted.

Following the 2001 International Sepsis Definition Conference, the Surviving Sepsis Campaign (SSC) was established. The goal of this campaign was to reduce mortality from sepsis via a 7-point agenda: building awareness of sepsis, improving diagnosis, increasing the use of appropriate treatment, educating healthcare professionals, improving post-ICU care, developing guidelines of care, and implementing a performance improvement program.[22]

It should be noted, however, that the definitions put forward and the overall campaign efforts were developed specifically for non-pregnant patients. Normal pregnancy is associated with an increase in heart rate, a decrease in diastolic blood pressure as a result of decreased systemic vascular resistance, an increased leukocyte count, and a decreased central venous pressure.[23–28] There is therefore considerable overlap between the SIRS criteria and normal physiologic parameters during pregnancy (see Table 3).[27]

**Table 1. Definition of sepsis[a]**

| Diagnosis | Definition |
|---|---|
| Bacteremia | Presence of viable bacteria in the blood |
| SIRS | Widespread inflammatory response defined by 2 or more:<br>Temperature >38°C or <36°C<br>Heart rate >90 bpm<br>Respiratory rate >20/min or $Paco_2$ <32 mm Hg<br>White blood cell count >12 or <4/μL or >10% bandemia |
| Sepsis | SIRS + source of infection |
| Severe sepsis | Sepsis + Evidence of organ dysfunction, tissue hypoperfusion, or hypotension |
| Septic shock | Sepsis + Hypotension despite adequate fluid resuscitation |

Abbreviations: $Paco_2$, partial pressure of arterial carbon dioxide; SIRS, systemic inflammatory response syndrome;
[a]Definitions from Bone et al.[19]

**Table 2. Diagnostic criteria for sepsis[a]**

| Diagnosis | Value |
|---|---|
| *Sepsis* | |
| General variables | Fever (core temperature >38.3°C) |
| | Hypothermia (core temperature <36°C) |
| | Heart rate >90 bpm or >2 SD above normal range for age[b] |
| | Tachypnea |
| | Altered mental status |
| | Significant edema[b] or positive fluid balance (>20 mL/kg over 24 h) |
| | Hyperglycemia (glucose >120 mg/dL or 7.7 mmol/L without diabetes) |
| Inflammatory variables | Leukocytosis (WBC >12 000/μL)[b] |
| | Leukopenia (WBC <4000/μL) |
| | Normal WBC count with >10% immature forms |
| | Plasma C-reactive protein >2 SD above normal value[b] |
| | PCT >2 SD above normal value |
| *Severe sepsis* | |
| Oxygen dysfunction variables | Arterial hypoxemia ($Pao_2/Fio_2$ <300) |
| | Acute oliguria (UOP <0.5 mL/kg/h or 45 mmol/L for 2 h) |
| | Creatinine >2.0 mg/dL[b] |
| | Coagulation abnormalities (INR >1.5 or aPTT >60 s) |
| | Thrombocytopenia (platelet count <100 000/μL)[b] |
| | Hyperbilirubinemia (total bilirubin >2 mg/dL or 35 mmol/L) |
| Tissue perfusion variables | Hyperlactatemia (>2 mmol/L) |
| | Decreased capillary refill or mottling |
| Hemodynamic variables | Hypotension (SBP <90 mm Hg, MAP <65 mm Hg, or SBP decrease by 40 mm Hg)[b] |

Abbreviations: aPTT, activated partial thromboplastin time; INR, international normalized ratio; MAP, mean arterial pressure; PCT, plasma procalcitonin; SBP, systolic blood pressure; UOP, urine output; WBC, white blood cell.
[a]Adapted with permission from Levy et al.[21]
[b]Value can be affected by pregnancy.

Especially notable regarding utilization of the above definitions, and the treatment protocols described below, is the lower mean arterial pressure and lower central venous pressure seen in normal pregnancy, especially in the second and third trimesters.

## SEVERITY OF ILLNESS SCORING SYSTEMS

Based on the definitions put forth by the American College of Chest Physicians/Society of Critical Care Medicine, the SSC strongly advocated for the development of tools to assess the severity of sepsis and to enable early detection of cases at risk for rapid clinical deterioration.[29] Many disease severity scoring systems related to sepsis have, therefore, been developed for the general population, for use in both an emergency department and an ICU setting. While these tools have been validated to predict outcome in critically ill nonpregnant adults, they all either specifically excluded or did not mention pregnant women in the study design.

Subsequent studies that have evaluated the utility of these illness-severity scoring systems in critically ill obstetric patients demonstrate that they overestimate morbidity and mortality in pregnancy.[30–36] For example, Afessa and colleagues[30] evaluated the acute physiology and chronic health evaluation (APACHE) II scores of 74 consecutive pregnant women admitted to an ICU in Florida from 1991 to 1998. Based on APACHE II scores, predicted mortality was 18% for this cohort, but in actuality, it was only 3%. In a larger study from Argentina, Vasquez et al[31] reported outcomes for 161 pregnant women admitted to an ICU from 1998 to 2005. Based on APACHE II scores, predicted mortality was 24%, whereas actual mortality was 11%. Other studies have demonstrated similar findings with APACHE II, APACHE III, and the Simplified Acute Physiology Score (SAPS) II.[32–34]

Use of the SIRS criteria outside of pregnancy is considered an accurate and reliable prediction of sepsis-related morbidity and mortality. In pregnancy and the puerperal period, this is a goal not yet realized, likely because of the considerable overlap between the SIRS criteria and the normal physiologic parameters during pregnancy and the postpartum period.[27] Lappen and coworkers[35] evaluated the predictive value of SIRS and the Modified Early Warning Score, a nonspecific disease severity score, in 913 pregnant women with chorioamnionitis. Specifically, they assessed whether either of these sets of criteria accurately identified disease progression as defined by ICU transfer, sepsis, or death. Five women in the cohort progressed to sepsis and 1 died. Two-thirds of women met SIRS criteria, which had only a 1% positive predictive value for disease progression. Ten percent had a Modified Early Warning Score of at least 5 (a commonly used threshold outside of pregnancy) and the positive predictive value for this prediction of ICU transfer, sepsis, or death was also very low—0.05%. Recently, Edwards and colleagues[36] sought to evaluate the predictive ability of published modified obstetric early warning scoring systems. These scoring systems again performed poorly and in general, overdetected severe sepsis.

Although there are several explanations for the poor performance of these scoring systems in pregnancy, 2 are most significant: the test performance characteristics and normal maternal physiologic changes of pregnancy. Because pregnant women are generally young and without chronic medical conditions, SIRS- and sepsis-related morbidity and mortality are lower in pregnant women than those in the generally older and sicker nonpregnant patients in whom the scoring systems were validated. As is the case for any test, with a lower prevalence of a condition (in this case, disease progression), there is a lower positive predictive value of the test. Normal physiological changes seen in pregnancy increase the scores for all existing, validated scoring systems, thereby biasing the scores to be worse. A 2014 commentary supports the use of early warning systems to facilitate timely recognition, diagnosis, and treatment of pregnant women developing a critical illness and proposes general criteria, the Maternal Early Warning Criteria.[37] These criteria, however, have yet to be validated and are not disease-specific. Therefore, identification and prompt treatment of

**Table 3. Normal values of pregnancy[a]**

| Value | Change from nonpregnant state |
|---|---|
| Temperature | Unchanged |
| Blood pressure | Systolic: Unchanged<br>Diastolic: Decrease by 5-10 mm Hg in second trimester, return to normal by third trimester |
| Heart rate | 83 ± 10 beats per minute (↑ 17%) |
| Respiratory rate | Unchanged |
| $O_2$ Saturation | Unchanged |
| Leukocyte count | 5.7-16.9/$\mu$L by third trimester (up to 30/$\mu$L in labor) |
| % Immature neutrophils | Unchanged |
| Lactic acid | Unknown |
| Central venous pressure | Nonpregnant: 9.0 cm $H_2O$ (7.8-11.2)<br>First trimester: 7.5 cm $H_2O$ (6.5-8.2)<br>Second trimester: 4.0 cm $H_2O$ (3.6-4.6)<br>Third trimester: 3.8 cm $H_2O$ (2.0-4.4) |

[a]Reference values from Cunningham et al[23]; Guinn et al[24]; Abbassi-Ghanavati et al[25]; Colditz and Josey[26]; Bauer et al[27]; and Clark et al.[28]

sepsis in pregnancy will remain imprecise until either alternative "SIRS" criteria or a pregnancy-specific sepsis scoring system is developed. One such scoring system has been proposed, the Sepsis in Obstetrics Score,[38] but has not yet been validated.

As disease severity scoring systems have to this point been largely unsuccessful in identifying pregnant women at highest risk of progression to severe sepsis and septic shock, investigators have begun to evaluate additional modifiable and nonmodifiable risk factors. These risk factors for progression to severe sepsis include non-Caucasian race, those with public insurance or no insurance, delivery at a low-volume hospital (<1000 births per year), medical comorbidities such as diabetes and hypertension, and pregnancy-related complications such as preeclampsia and postpartum hemorrhage.[39,40] While many of these cannot be changed, increased vigilance in the setting of these risk factors is warranted.

## COMMON CAUSES OF SEPSIS IN PREGNANCY

In addition to uterine sources for sepsis, common sites of infection in pregnant women are similar to those in nonpregnant adults with sepsis: the urinary tract, the respiratory tract, and the abdomen. In pregnancy, the most common causes of sepsis include endometritis and chorioamnionitis or "puerperal sepsis" (2.5%-58%), urinary tract infections including pyelonephritis (1.3%-33.3%), and pneumonia (2.5%-29.7%).[11–13,41–43] In nonpregnant adults with sepsis, gram-positive bacteria account for approximately 52% and polymicrobial infections account for 5% of cases.[2,44] Conversely, infections that result in sepsis in pregnancy are commonly polymicrobial, reflecting the anatomic continuity with the vaginal flora[41] or from gram-negative bacteria such as *Escherichia coli*, which often arises from a urinary source.[12,13,43]

However, there has been an increase in severe $\beta$-hemolytic streptococci group A (GAS) infections, leading to increased morbidity and mortality.[43,45] In a study from the Netherlands, the organisms most commonly identified which resulted in obstetric sepsis were $\beta$-hemolytic streptococci group A (GAS) (31.8%) and *E coli* (11.4%).[42] In women whose deaths were directly attributed to sepsis, 7 of 16 were a result of GAS and 5 of 16 were a result of *E coli*. Despite its rarity, and because management of sepsis caused by GAS must be aggressive and requires a specific management algorithm, identification or exclusion of this organism as a cause of maternal sepsis must be a priority among providers evaluating pregnant or postpartum women with sepsis-type symptoms.[45]

## MANAGEMENT OF SEPSIS

### Early goal-directed therapy

Early goal-direct therapy (EGDT) includes early initiation and continuation of hemodynamic resuscitation with specified treatment endpoints and was first shown to have a mortality benefit in the sentinel study by Rivers et al[46] in 2001. Study participants allocated to EGDT were significantly less likely to die in the hospital, 30.5% versus 46.5% (relative risk [RR]: 0.58, 95% confidence interval: 0.38-0.87), and less likely to have experienced mortality 28 and 60 days after enrollment (33.3% and 44.3% vs 49.2% and 56.9%; RR: 0.58, 95% confidence interval: 0.39-0.87 and RR: 0.67, 95% confidence interval: 0.46-0.96, respectively). Early studies following EGDT implementation have shown a close to 20% decrease in overall mortality for septic patients.[47–49] However, 3 recently published randomized controlled trials evaluating EGDT versus usual care did not show a mortality benefit with EGDT.[50–52] This is likely due to the fact that usual care now includes aggressive, early fluid resuscitation and rapid administration of appropriate antibiotics, which reflect the impact of the original trial by Rivers and colleagues.[46] In addition, mortality rates in both groups were impressively low in all 3 studies (18.8%-29.2%) indicating effective treatment.[50–52] Therefore, the continued use of EGDT in management of sepsis is recommended.[49,53,54]

Specifically, EGDT is aimed at correcting the physiologic abnormalities that accompany sepsis, including hypotension and hypoxemia, to improve tissue oxygen delivery. This includes early initiation of antimicrobial therapy (described alter) as well as aggressive hemodynamic resuscitation.

The recommendations for resuscitation have been integrated into SSC Bundles. The bundles are the core of the sepsis improvement efforts and aim to simplify and streamline the care of men and women with sepsis. A bundle is a selected set of elements that, when implemented as a group, have an effect on outcomes beyond implementing the individual elements alone.

The current bundles are designed to be completed within a set period of time following an individual's presentation with severe sepsis or septic shock.[29,49] These bundles are described in Table 4.

It is necessary to realize that the above bundles do not have to be solely physician-driven. In fact, with the implementation of a nurse-initiated emergency department sepsis protocol, compliance with serum lactate measurement and blood culture collection within 3 hours approached 100% in one study[55] and improved significantly in another.[56]

Table 4. **Surviving sepsis campaign bundles**[a]

| Time Frame | Actions |
|---|---|
| To be completed within 3 h | 1. Measure lactic acid level<br>2. Obtain blood cultures prior to administration of antibiotics<br>3. Administer broad-spectrum antibiotics<br>4. Administer 30 mL/kg crystalloid for hypotension or lactic acid ≥4 mmol/L |
| To be completed within 6 h | 1. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a MAP ≥65 mm Hg (eg, norepinephrine)<br>2. In the event of persistent hypotension after initial fluid administration (MAP < 65 mm Hg) or if initial lactic acid was ≥4 mmol/L, reassess volume status and tissue perfusion<br>3. Remeasure lactic acid if initially elevated |

Abbreviation: MAP, mean arterial pressure.
[a]From Dellinger et al[29] and Levy et al[49]

## Pregnancy-specific issues with goal-directed therapy

No trials of EGDT have been conducted among pregnant women. It, therefore, remains unclear whether EGDT improves the outcomes of pregnant women with sepsis. Extrapolating EGDT to pregnant women is not straightforward because of the normal physiologic changes that occur in pregnancy, but in order to effectively utilize EGDT in pregnant women, these physiologic changes need to be taken into consideration.

Until clinical management trials examining the effectiveness of EGDT in pregnancy are undertaken, development of sepsis protocols for peripartum women will be extrapolations rather than data-driven. However, utilization of the aforementioned sepsis bundles is likely appropriate and must be prioritized.[57] Notably, one study demonstrated that elevated lactic acid in pregnancy was associated with adverse maternal outcomes from sepsis, highlighting the significance of that measurement.[58] In addition, while use of acetaminophen for fever in the critically ill with suspected infections has not shown a mortality or morbidity benefit,[59] its use in pregnancy is crucial as maternal fever can result in fetal tachycardia and subsequent fetal compromise.[60]

## Antimicrobial therapy

Along with aggressive resuscitation, early initiation of appropriate antibiotic therapy is a critical determinant of survival in sepsis and septic shock. A large retrospective study by Kumar et al[61] among nonpregnant adults with sepsis demonstrated that time to initiation of antibiotic therapy was the strongest predictor of mortality. Initiation of antibiotics within 1 hour following the onset of hypotension was associated with a 79.9% survival to hospital discharge. For every hour delay in the first 6 hours, survival declined by 7.6%. Other studies have also shown a mortality benefit with early initiation of antibiotics.[46,62–65]

Initial administration of inappropriate antibiotic therapy increases morbidity and mortality, with up to a 5-fold increase in mortality.[65–67] Therefore, because the infecting organism is likely not known at the time of antibiotic initiation, empiric regimens need to err on the side of broader spectrum and be based on clinical presentation and epidemiologic factors, including local flora, resistance patterns, and previous antibiotic exposure. Accordingly, the choice of antibiotic may differ for a pregnant or postpartum woman depending upon the suspected source of sepsis. Involvement of obstetricians and maternal-fetal medicine specialists is paramount in the care of such critically ill patients, because of such specialists' familiarity with the organisms known to cause sepsis in pregnancy and the puerperium.

In severe infections, survival may be improved if the organism(s) can be isolated. It is, therefore, necessary to obtain site-specific cultures to allow for identification and susceptibility testing. Empiric antibiotic therapy can then be adjusted to a narrower regimen within 48 to 72 hours if a plausible pathogen is identified or if the woman stabilizes. If the source of infection is known or suspected, targeted antibiotic coverage is appropriate initially. Common causes of sepsis in pregnant and postpartum women with suggested site-specific antibiotic coverage are listed in Table 5.[29,68–71]

## Source control

The term "source control" is used to define the spectrum of interventions whose objective is the physical control of infection. Successful management of sepsis requires early and appropriate antibiotic therapy and aggressive fluid resuscitation, as well as source control. Antibiotic therapy is critical to initiate prior to any attempt at source control.[29]

The cardinal principles of source control include drainage of infected fluid collections, debridement of infected solid tissue, removal of devices or foreign bodies, and definitive measures to correct anatomic derangements resulting in ongoing microbial

Table 5. **Common causes of sepsis and suggested antibiotic coverage**[a]

| Cause | Causative organism | Suggested antibiotic coverage |
|---|---|---|
| Endometritis | Polymicrobial: Mixture of 2-3 genital tract aerobes and anaerobes | Broad-spectrum parenteral antibiotics that include coverage for β-lactamase producing anaerobes<br>• Clindamycin 900 mg IV every 8 h + Gentamicin 5 mg/kg every 24 h *or* 1.5 mg/kg IV every 8 h |
| Intra-amniotic infection | Polymicrobial, primarily due to ascending colonization or infection | Broad-spectrum parenteral antibiotics with coverage for β-lactamase producing aerobes and anaerobes<br>• Ampicillin 2 g every 6 h + Gentamicin 1.5 mg/kg every 8 h for patients with normal renal function<br>• Add clindamycin 900 mg or metronidazole 500 mg to the primary antibiotic regimen if the patient is undergoing a cesarean delivery<br>• Penicillin allergy: Substitute vancomycin 1 g every 12 h for ampicillin |
| Urinary tract infections | *E coli*, *Klebsiella* or *Enterobacter*, *Proteus*, and gram-positive organisms, including *Streptococcus agalactiae* | Parenteral β-lactams<br>• Avoid fluoroquinolones<br>• Ceftriaxone 1-2 g every 24 h *or* ampicillin 1-2 g every 6 h + Gentamicin 1.5 mg/kg every 8 h |
| Group A streptococcus | *S pyogenes* | Parenteral β-lactam + Clindamycin<br>• Penicillin G 4 million units IV every 4 h + Clindamycin 900 mg IV every 8 h<br>• Consider IV immune globulin with worsening |
| Community-acquired pneumonia | Bacterial: *S pneumonia, K pneumonia, Haemophilus influenza, Pseudomonas aeruginosa, Staphylococcus aureus*<br>Viral: Influenza | Parenteral antipneumococcal β-lactam + Advanced macrolide ± Antiviral<br>• Avoid fluoroquinolones<br>• Ceftriaxone 1-2 g daily, cefotaxime 1-2 g every 8 h, *or* ampicillin-sulbactam 1.5-3 g every 6 h + Azithromycin 500mg daily<br>• Antiviral: Oseltamivir 75 mg PO every 12 h |
| Septic abortion | Polymicrobial | Parenteral broad-spectrum antibiotics<br>• Clindamycin 900 mg every 8 h + Gentamicin 5 mg/kg daily ± Ampicillin 2 g every 4 h; *or* Ampicillin + Gentamicin + Metronidazole 500 mg every 8 h; *or* levofloxacin 500 mg daily and metronidazole; *or* single agents such as Ticarcillin-clavulanate 3.1 g every 4 h piperacillin-tazobactam 4.5 g every 6 h, or imipenem 500 mg every 6 h |
| Necrotizing fasciitis | Polymicrobial | Surgical debridement + Broad-spectrum antimicrobial therapy, including activity against gram-positive, gram-negative, and anaerobic organisms, with special consideration for group A streptococcus and *Clostridium* species<br>• Carbapenem or β-lactam/β-lactamase inhibitor + clindamycin 600-900 mg every 8 h, for its antitoxin effects against toxin-elaborating strains of streptococci and staphylococci), as well as an agent with activity against methicillin-resistant *S aureus* (such as vancomycin, daptomycin, or linezolid)<br>• Options for carbapenems: Imipenem, meropenem, or ertapenem<br>• Options for β-lactam/β-lactamase inhibitors: Piperacillin/tazobactam, ampicillin/sulbactam, or ticarcillin/clavulanate<br>• Patients with hypersensitivity to these agents may be treated either with an aminoglycoside or a fluoroquinolone, plus metronidazole |
| Toxic shock syndrome | *S aureus* | • Clindamycin 600 mg IV every 8 h + Vancomycin 30 mg/kg/d IV in 2 divided doses<br>• Unclear whether antibiotics alter the course, however, needed to eradicate organisms and prevent recurrence |

Abbreviations: IV, intravenously; PO, by mouth.

[a]Recommendations are expert opinion (Dr Brenna Hughes) in accordance with the Infectious Diseases Society of America guidelines.[29,68–71]

contamination to restore optimal function.[72] Drainage, debridement, and removal of foreign bodies must occur as soon as possible in sepsis care.[72,73]

While there are no randomized trials comparing techniques of abscess drainage, the optimal method is that which accomplishes full drainage with the least degree of anatomic and physical trauma. In the setting of retained products of conception, dilation/curettage is indicated. The surgical tenet of source control is never more crucial than it is in the case of GAS puerperal sepsis. In this setting of a mortality rate of approximately 50%, hysterectomy can be lifesaving.[45]

## Blood product administration

Anemia in those with early severe sepsis and septic shock often results from a combination of preexisting disease and acute volume resuscitation.[74] The combination of anemia and the presence of global tissue hypoxia in the hypotensive septic patient support the rationale for red blood cell transfusion to increase oxygen delivery. Although the optimum hemoglobin concentration for adults with severe sepsis has not been specifically investigated, the international guidelines for the SSC published in 2012 recommend transfusion to a target of 7 to 9 g/dL in adults based largely on the Transfusion Requirements in Critical Care Trial.[29,75] The Transfusion Requirements in Critical Care Trial found that a restrictive strategy of red cell transfusion (to a target of 7-9 g/dL) is at least as effective as and possibly superior to a liberal transfusion strategy in those who are critically ill with similar overall 30-day mortality in the 2 groups (18.7% vs 23.3%, $P = .11$) and mortality rate during hospitalization significantly lower in the restrictive-strategy group (22.3% vs 28.1%, $P = .05$).[75]

Erythropoietin is not recommended as there is no evidence that it improves outcomes.[76] There are limited studies evaluating platelet transfusion in a critical care setting, and guidelines are derived from consensus opinion and experience in individuals undergoing chemotherapy. Extrapolating from the oncology literature, platelet transfusion may be indicated with significant thrombocytopenia at risk for spontaneous bleeding ($<5000/mm^3$) regardless of apparent bleeding.[77] Platelet transfusion may be considered when counts are 5000 to 30 000/$mm^3$ and there is a significant risk of bleeding. Higher platelet counts ($>50\,000/mm^3$) are typically required for surgery or invasive procedures.[29] Finally, clinical studies have not assessed the impact of fresh frozen plasma on outcomes in those who are critically ill, and such therapy is not recommended in the absence of bleeding or planned invasive procedures.

## Glucose control

While the current sepsis guidelines from the SSC recommend maintaining glucose levels of less than 150 mg/dl, this recommendation has since been questioned.[29] In contrast with earlier studies among critically ill patients, recent studies have not found a benefit of intensive glucose control in adults with sepsis.[78,79] A meta-analysis including 26 trials (13 567 participants) concluded that intensive insulin therapy conferred no overall mortality benefit among the critically ill but did significantly increase the risk of hypoglycemia.[78] A more recent publication from the NICE-SUGAR Study Investigators demonstrates that intensive glucose control leads to moderate and severe hypoglycemia, both of which are associated with death and exhibit a dose-response relationship (the more severe the hypoglycemia, the stronger the association).[79] Current evidence does not allow for a confident formulation of targets in glucose management in sepsis.

While there are no studies evaluating maternal glycemic control in a critical care setting, these values are well-defined outside of the ICU. The American Congress of Obstetricians and Gynecologists recommends that women with gestational, type 1 or type 2 diabetes be monitored closely with 4-times daily blood glucose checks with goal blood sugars of less than 95 mg/dL fasting and less than 120 mg/dL 2-hour postprandial.[80,81]

In general, maternal hyperglycemia results in fetal hyperglycemia and fetal osmotic diuresis. The fetus can become acidotic from keto acids that cross the placenta. Acidemia decreases uterine blood flow, reduces tissue perfusion, and leads to decreased fetal oxygenation. Therefore, late decelerations and decreased fetal heart rate variability are common findings on fetal heart rate monitoring during an acute hyperglycemic episode. Fetal testing will improve as maternal hyperglycemia and acidemia improve.

Cases of acute, severe hyperglycemia, most commonly diabetic ketoacidosis, pose an immediate threat to maternal well-being, similar to nonpregnant adults. Fetal well-being in maternal ketoacidosis is also threatened. A single episode of ketoacidosis can have a perinatal mortality rate of 9% to 35%.[82,83]

## Venous thromboembolism prophylaxis

The presence of venous thromboembolism (VTE) or pulmonary embolism adversely affects morbidity and mortality in the critically ill.[84,85] Unfortunately, there are no studies evaluating mechanical thromboprophylaxis in the ICU setting. However, pharmacologic VTE prophylaxis, either low-molecular-weight heparin or unfractionated heparin, is effective at preventing VTE and

pulmonary embolism in critically ill patients.[85] The cost of low-molecular-weight heparin is higher but the frequency of administration is lower. Unfractionated heparin is preferred over low-molecular-weight heparin in those with moderate to severe renal dysfunction. Three times a day dosing of unfractionated heparin produces better efficacy and twice daily dosing produces less bleeding, arguing for individualization in dosing based on the underlying risk of VTE and bleeding.[86] Mechanical methods are recommended when pharmacologic anticoagulation is contraindicated. Studies examining the effectiveness of VTE prophylaxis among critically ill pregnant women are lacking.

### Stress ulcer prophylaxis

Stress ulcer prophylaxis prevents serious gastrointestinal bleeding in those who are critically ill; however, it may not prevent death.[87] It has also been associated with an increased risk of ventilator-associated pneumonia and *Clostridium difficile* infections.[88] Nevertheless, stress ulcer prophylaxis is recommended in the setting of severe septic shock. Both proton pump inhibitors and histamine-2 receptor antagonists are considered equal in efficacy and both are safe in pregnancy.[89]

## PREGNANCY-SPECIFIC GOALS OF SEPSIS MANAGEMENT

The overall goal of EGDT, manipulation of cardiac preload, afterload, and contractility to achieve a balance between systemic oxygen delivery and oxygen demand, is a good general tenet of care and, in pregnancy, is one that aids in the restoration of normal maternal and fetal physiologic functioning. A management algorithm for pregnant women cannot be specifically advocated until adequate studies are performed, but clearly any algorithm requires standard EGDT and fetal assessment. Maternal sepsis is associated with an increased risk of preterm delivery, low birth weight, and perinatal mortality.[90,91] Notably, fetal mortality approaches 33% in the setting of maternal sepsis, requiring ICU admission.[92]

When a pregnant woman presents with sepsis, general medical principles hold. The first goal is to establish circulation, airway, and breathing to ensure maternal stability. Once maternal stability is ensured, if the pregnancy is beyond viability (traditionally beyond 24 weeks' gestation; however, in certain centers, this is changing to 23 weeks' gestation[93,94]), a fetal monitor is applied. With maternal stabilization plus either a reactive nonstress test or biophysical profile of 8 or greater, fetal monitoring can be performed intermittently. Below the limit of viability, a fetal heart rate only is documented.

Fetal heart rate tracings may demonstrate evidence of fetal acidemia with presence of late decelerations. Additional maneuvers may need to be employed in a pregnant woman with sepsis including left uterine displacement in order to aid in fetal resuscitation. Caution is necessary when monitoring a viable fetus in a critically ill woman because maternal stability is always the primary goal. Attempts to deliver an acidemic fetus may worsen a mother's condition and result in prematurely delivering a fetus who may have recovered with adequate resuscitation in utero. In the setting of maternal sepsis, fetal optimization is frequently best accomplished by meeting maternal hemodynamic, oxygenation, and infection treatment goals.[95] As maternal acidemia and/or hypoxia resolves, fetal status will improve.

A recent study evaluated indications for delivery in women presenting with severe sepsis and septic shock.[96] They found that one-third of women with severe sepsis and all women presenting with septic shock required delivery during the same hospitalization, most requiring emergent delivery. The most common indication for delivery was worsening respiratory status.

Delivery in the setting of respiratory failure will almost necessarily be via Cesarean. In the setting of sepsis that develops during labor, aggressive maternal treatment followed by attempted vaginal delivery will likely benefit both mother and fetus. Finally, delivery within 5 minutes following a maternal cardiac arrest is vital for both maternal and fetal benefit.[97]

## CONCLUSION

Maternal morbidity and mortality appear to be on the rise in the United States. While the diagnosis and management of sepsis has been well-established in a nonpregnant population, the ability to apply that same level of expertise to pregnant women is hindered by the lack of data surrounding sepsis in obstetrics. Pregnancy poses a unique challenge given the baseline physiologic changes and the need to care for the mother while simultaneously caring for the fetus. Therefore, without clear pregnancy-specific data, recommendations are to follow the current guidelines for nonpregnant adults while being cognizant of the ways in which pregnancy may change the goals of management. Prompt identification and treatment of maternal sepsis will undoubtedly lead to the best possible maternal and neonatal outcomes.

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