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Society for Maternal-Fetal Medicine Consult Series #67: Maternal sepsis

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Maternal sepsis is a significant cause of maternal morbidity and mortality, and is a potentially preventable cause of maternal death. This Consult aims to summarize what is known about sepsis and provide guidance for the management of sepsis during pregnancy and the postpartum period. Most studies cited are from the nonpregnant population, but where available, pregnancy data are included. The following are the Society for Maternal-Fetal Medicine recommendations: (1) we recommend that clinicians consider the diagnosis of sepsis in pregnant or postpartum patients with otherwise unexplained end-organ damage in the presence of a suspected or confirmed infectious process, regardless of the presence of fever (GRADE 1C); (2) we recommend that sepsis and septic shock in pregnancy be considered medical emergencies and that treatment and resuscitation begin immediately (Best Practice); (3) we recommend that hospitals and health systems use a performance improvement program for sepsis in pregnancy with sepsis screening tools and metrics (GRADE 1B); (4) we recommend that institutions develop their own procedures and protocols for the detection of maternal sepsis, avoiding the use of a single screening tool alone (GRADE 1B); (5) we recommend obtaining tests to evaluate for infectious and noninfectious causes of life-threatening organ dysfunction in pregnant and postpartum patients with possible sepsis (Best Practice); (6) we recommend that an evaluation for infectious causes in pregnant or postpartum patients in whom sepsis is suspected or identified includes appropriate microbiologic cultures, including blood, before starting antimicrobial therapy, as long as there are no substantial delays in timely administration of antibiotics (Best Practice); (7) we recommend obtaining a serum lactate level in pregnant or postpartum patients in whom sepsis is suspected or identified (GRADE 1B); (8) in pregnant or postpartum patients with septic shock or a high likelihood of sepsis, we recommend administration of empiric broad-spectrum antimicrobial therapy, ideally within 1 hour of recognition (GRADE 1C); (9) after a diagnosis of sepsis in pregnancy is made, we recommend rapid identification or exclusion of an anatomic source of infection and emergency source control when indicated (Best Practice); (10) we recommend early intravenous administration (within the first 3 hours) of 1 to 2 L of balanced crystalloid solutions in sepsis complicated by hypotension or suspected organ hypoperfusion (GRADE 1C); (11) we recommend the use of a balanced crystalloid solution as a first-line fluid for resuscitation in pregnant and postpartum patients with sepsis or septic shock (GRADE 1B); (12) we recommend against the use of starches or gelatin for resuscitation in pregnant and postpartum patients with sepsis or septic shock (GRADE 1A); (13) we recommend ongoing, detailed evaluation of the patient's response to fluid resuscitation guided by dynamic measures of preload (GRADE 1B); (14) we recommend the use of norepinephrine as the first-line vasopressor during pregnancy and the postpartum period with septic shock (GRADE 1C); (15) we suggest using intravenous corticosteroids in pregnant or postpartum patients with septic shock who continue to require vasopressor therapy (GRADE 2B); (16) because of an increased risk of venous thromboembolism in sepsis and septic shock, we recommend the use of pharmacologic venous thromboembolism prophylaxis in pregnant and postpartum patients in septic shock (GRADE 1B); (17) we suggest initiating insulin therapy at a glucose level >180 mg/dL in critically ill pregnant patients with sepsis (GRADE 2C); (18) if a uterine source for sepsis is suspected or confirmed, we recommend prompt delivery or evacuation of uterine contents to achieve source control, regardless of gestational age (GRADE 1C); and (19) because of an increased risk of physical, cognitive, and emotional problems in survivors of sepsis and septic shock, we recommend ongoing comprehensive support for pregnant and postpartum sepsis survivors and their families (Best Practice).

Key words: end-organ damage, infection, maternal sepsis, pregnancy-associated sepsis, resuscitation, screening, sepsis, septic shock, vasopressors

Introduction

Sepsis and septic shock are medical emergencies that are increasingly recognized as important and preventable causes of maternal death. In the United States, sepsis is now the second leading cause of maternal death, accounting for 13.9% of all pregnancy-related deaths[1] despite complicating only 4 per 10,000 live births.[2–5] Delays in recognizing and managing sepsis are common in the obstetrical population.[6,7] In 63% of maternal sepsis deaths, independent reviewers found substandard care, most often a delay in recognition or management, particularly on the obstetrical unit.[7]

The rate of maternal sepsis seems to be increasing. A detailed analysis of pregnancy-associated sepsis during a delivery hospitalization in Texas demonstrated a temporal increase in pregnancy-associated severe sepsis, doubling from 6 per 10,000 in 2001 to 12 per 10,000 in 2010.[8] When abortions and fetal demises were included, the incidence of pregnancy-associated severe sepsis increased from 11 per 10,000 pregnancies in 2001 to 26 per 10,000 in 2010.[8] There was a 9.1% annual increase in sepsis as the maternal cause of death from 2001 to 2010.[8] Similarly, an evaluation of the Nationwide Inpatient Sample between 1998 and 2008 demonstrated a 10%-per-year increase in maternal sepsis and sepsis-related death in the United States.[9] Nulliparity, the lived experience of anti-Black racism, and public or no insurance have been identified as risk factors for pregnancy-associated sepsis.[10,11] In addition, obstetrical risk factors, including cesarean delivery, assisted reproductive technologies, and multiple gestation may play a role.[12,13] More than 50% of the pregnant patients who die from sepsis have ≥1 chronic comorbid conditions, such as chronic renal disease, chronic liver disease, or congestive heart failure.[8,12]

In 2002, the Surviving Sepsis Campaign (SSC) was launched with the goal of reducing sepsis and septic shock.[14] The SSC developed evidence-based management guidelines and promoted their integration into resuscitation and management bundles. There was a major update to the guidelines in 2016[15] with the Third International Consensus Definitions,[16] which streamlined definitions and clinical criteria, eliminating use of the terms "severe sepsis" or "systematic inflammatory response syndrome (SIRS)" to avoid errors in diagnosis and classification, and to promote greater consistency for epidemiology and clinical trials. In 2021, the new SSC guidelines provided up-to-date, evidence-based guidance for clinicians treating adult patients with sepsis or septic shock.[17] The purpose of this Consult is to summarize what is known about maternal sepsis and provide the latest guidance for the management of sepsis during pregnancy and the postpartum period incorporating the new SSC guidelines.

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How is sepsis defined, and how do the clinical features differ during pregnancy and the postpartum period?

Sepsis is not a specific illness but a nonlinear, complex syndrome that encompasses a still uncertain pathobiology. The present categories established by the Third International Consensus Definitions for Sepsis and Septic Shock Task Force in 2016 emphasize signs of organ dysfunction rather than signs of infection.[16] The Task Force defines sepsis as "life-threatening organ dysfunction caused by a dysregulated host response to infection."[16] Organ dysfunction may be objectively defined as an acute increase of ≥2 points in the Sequential Organ Failure Assessment (SOFA) score (Table 1).[18] The initial SOFA score should be zero in individuals without disease. Although multiple definitions for septic shock are currently in use, septic shock is defined by the Septic Shock Task Force[16] as a "subset of sepsis in which underlying circulation and cellular/metabolic abnormalities are profound enough to substantially increase mortality." Septic shock can be identified within a clinical construct of sepsis with persistent hypotension requiring vasopressors to maintain mean arterial pressure (MAP) ≥65 mm Hg and a serum lactate level >2 mmol/L despite adequate volume resuscitation.[16]

The World Health Organization (WHO) launched the Global Maternal and Neonatal Sepsis Initiative to "focus additional efforts, energize stakeholders and accelerate progress in the area of maternal and neonatal infection."[19] The WHO definition of maternal sepsis is now "a life-threatening condition defined as an organ dysfunction caused by an infection during pregnancy, delivery, puerperium, or after an abortion."[19] The Global Maternal and Neonatal Sepsis Initiative also recommended that clinicians avoid using imprecise and potentially misleading terms such as maternal infection, puerperal sepsis, and postpartum sepsis.[19]

Normal human pregnancy is a state of expanded plasma volume, increased cardiac output, and peripheral vasodilation. None of the existing definitions of sepsis account for the physiological alterations of normal pregnancy. Importantly, fever is neither necessary nor sufficient to determine whether sepsis is present, and normal physiological changes of pregnancy significantly affect early recognition of sepsis. When nonpregnant norms are used, overdiagnosis or underdiagnosis of sepsis may occur. Of the SOFA criteria, those most affected by pregnancy are creatinine and MAP. The SOFA score assigns a point value above zero once serum creatinine reaches 1.2 mg/dL, but this level is well above the upper limit of normal in normal pregnancy. In addition, the SOFA score considers a MAP <70 abnormal, whereas this level may be physiological in the second trimester. An analysis of normal maternal physiological parameters[20] showed that sepsis cutoffs for respiratory rate, heart rate, partial pressure of CO_2, and white blood cell count overlapped with the normal range for pregnancy, labor, and the early postpartum period.

TABLE 1
Sequential Organ Failure Assessment score[18]

Organ system	Score 0	1	2	3	4
Respiratory					
PaO_2/F_IO_2	≥400 mm Hg (53.3 kPa)	<400 mm Hg (53.3 kPa)	<300 mm Hg (40 kPa)	<200 mm Hg (26.7 kPa) with respiratory support	<100 mm Hg (13.3 kPa) with respiratory support
Coagulation					
Platelets	≥150×10^3/μL	<150	<100	<50	<20
Hepatic					
Bilirubin	<1.2 mg/dL (20 μmol/L)	1.2–1.9 mg/dL (20–32 μmol/L)	2.0–5.9 mg/dL (33–101 μmol/L)	6.0–11.9 mg/dL (102–204 μmol/L)	>12 mg/dL (204 μmol/L)
Cardiovascular					
MAP	≥70 mm Hg	<70	Dopamine <5 μg/kg/min, or any dose of dobutamine	Dopamine 5.1–15 μg/kg/min, or epinephrine ≤0.1 μg/kg/min, or norepinephrine ≤0.1 μg/kg/min	Dopamine >15, or epinephrine >0.1, or norepinephrine>0.1
Central nervous system: Glasgow Coma Scale score	15	13–14	10–12	6–9	<6
Renal	Serum creatinine <1.2 mg/dL (110 μmol/L)	Serum creatinine 1.2–1.9 mg/dL (110–170 μmol/L)	Serum creatinine 2.0–3.4 mg/dL (171–299 μmol/L)	Serum creatinine 3.5–4.9 mg/dL (300–440 μmol/L) OR Urine output <500 mL/d	Serum creatinine >5.0 mg/dL (440 μmol/L) OR Urine output < 200 mL/d

F_IO_2, fraction of inspired oxygen; *MAP*, mean arterial pressure; *PaO_2*, partial pressure of oxygen.

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Making a diagnosis of sepsis in the early postpartum period can be extremely challenging because of external influences from normal and abnormal labor and delivery (eg, large fluid shifts, effects of regional anesthesia, postpartum hemorrhage, etc.), a rapid change in normal physiology in the first 2 weeks postpartum characterized by wide reference ranges for normal vital sign parameters, and a lack of studies on criteria to use for screening and diagnosing sepsis during this time. In a multicenter prospective longitudinal cohort study of >900 women, the median systolic and diastolic blood pressures increased by 5 mm Hg each by days 5 and 6 postpartum, then gradually returned to nonpregnant values by day 14 postpartum.[21] Maternal heart rate was highest on the day of birth at 84 beats per minute (bpm) and decreased to a median of 75 bpm on postpartum day 14.[21] Overlap between normal and abnormal ranges during pregnancy may lead to false-positive diagnoses. Conversely, the clinician may underreact to signs of sepsis, especially in the postpartum period, because they are accustomed to the presence of tachycardia or leukocytosis in normal pregnancy. **We recommend that clinicians consider the diagnosis of sepsis in pregnant or postpartum patients with otherwise unexplained end-organ damage in the presence of a suspected or confirmed infectious process, regardless of the presence of fever (GRADE 1C).**

What is the pathophysiology of sepsis?

Sepsis results from a dysregulated host response to infection resulting in organ damage, and virtually any organ system can be affected (Table 2). The excessive inflammatory response that occurs with sepsis includes extravasation of albumin and fluid, with resultant intravascular hypovolemia. Cytokine release leads to decreased systemic vascular resistance and increased cardiac output, although up to 60% of patients with sepsis have an ejection fraction <45% (systolic dysfunction). Septic cardiomyopathy may manifest with diastolic dysfunction because of cardiac edema and diminished compliance. The noncompliant left ventricle will cause decreased diastolic filling and reduced stroke volume, increasing the risk of pulmonary edema with excessive fluid resuscitation. Tissue ischemia (and dysfunction) results primarily from hypotension and from

TABLE 2
Organ damage caused by sepsis

System	Description of damage
Central nervous system	Altered mental status
Cardiovascular system	Hypotension from vasodilation and third-spacing; myocardial dysfunction
Pulmonary system	ARDS
Gastrointestinal system	Paralytic ileus
Hepatic system	Hepatic failure or abnormal transaminases
Urinary system	Oliguria or acute kidney injury
Hematologic system	Thrombocytopenia or disseminated intravascular coagulopathy
Endocrine system	Adrenal dysfunction and increased insulin resistance

ARDS, acute respiratory distress syndrome.
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microvasculature occlusion by microthrombi because of disseminated intravascular coagulation.

The pathogenesis of hyperlactatemia in septic states is complex. Lactic acid buildup is due to several different processes, including anaerobic metabolism in tissues, acceleration in glycolytic fluxes, inhibition of pyruvate dehydrogenase activity, changes in intermediary metabolism, and a decrease in lactate elimination.[22,23] The major source of excess lactate is the lung, and metabolic acidosis associated with hyperlactatemia is most likely related to the effect of the lactate ion on the acid-base balance and subsequently on the dissociation of plasma water into hydrogen ions.

What are the most common infectious etiologies of maternal sepsis?

The source of infection in maternal sepsis can be either pelvic or nonpelvic. The most common causes are presented in Table 3. Antepartum cases of sepsis are most commonly because of a genitourinary source, with pyelonephritis being the most common reason for antepartum nonobstetrical hospitalization.[4,10,12] Intrapartum and postpartum cases are more likely to have a genitourinary or respiratory source.[4,10,24] In 30% of cases, no source is identified.

TABLE 3
Common sources of infection in sepsis

Sources	Antepartum	Postpartum
Obstetrical	Septic abortion	Endometritis
	Chorioamnionitis	Wound infection
Nonobstetrical	Urinary tract infection	Urinary tract infection
	Pneumonia	Pneumonia
	Appendicitis	Gastrointestinal

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Microbiology is not specifically addressed in most reports of maternal sepsis. In the UK Obstetric Surveillance System, clinical laboratory testing identified the causative microorganism in only 64% of maternal sepsis cases, and the clinician identified the source in only 74%. In 16%, neither the inciting organism nor the source of sepsis was identified.[25] These figures are consistent with the overall experience of sepsis in a general adult population, in which blood cultures are negative in two-thirds of patients and cultures from all sites are negative in one-third.[26]

The most frequently isolated organisms in maternal sepsis are *Escherichia coli* and group A and group B *Streptococcus*.[13,25] However, staphylococci, gram-negative and anaerobic bacteria, and many other organisms have been reported.[24,27] Mixed infections are also possible; in 15% of maternal sepsis deaths in which organisms could be identified, the infection was polymicrobial.[28]

How is sepsis recognized in pregnancy?

Early recognition of sepsis in pregnant and postpartum patients is critical to reducing severe morbidity and mortality. The first step in recognition is educating patients on the urgent maternal warning signs of medical emergencies, including sepsis. It is critical to build trust with patients early in pregnancy so they are comfortable sharing concerns. The Centers for Disease Control and Prevention *Hear Her* Campaign has several open-source materials available to facilitate proactive patient education.[29] As detailed in the provider-facing resources of the *Hear Her* Campaign, health care professionals must listen and adequately address concerns when patients report relevant symptoms. **We recommend that sepsis and septic shock in pregnancy be considered medical emergencies and that treatment and resuscitation begin immediately (Best Practice).**[17]

Performance improvement programs that include sepsis screening tools and metrics result in better adherence to sepsis bundles and a reduction in mortality in the nonpregnant, general population (odds ratio [OR], 0.66; 95% confidence interval [CI], 0.61−0.72).[30] **We recommend that hospitals and health systems use a performance improvement program for sepsis in pregnancy with sepsis screening tools and metrics (GRADE 1B).**[17]

Various tools are used to predict death and prolonged intensive care unit (ICU) stays in nonobstetrical patients. For example, a brief bedside assessment tool known as the quick SOFA score (qSOFA) has been introduced into clinical practice.[16] The qSOFA score evaluates the presence of 3 clinical criteria: systolic blood pressure $\leq$100 mm Hg, respiratory rate $\geq$22 per minute, and altered mental status. If $\geq$2 of these criteria are present, the patient is at increased risk

for poor sepsis-related outcomes. These signs should prompt the physician to look carefully for organ dysfunction, start or escalate therapy, increase the acuity of monitoring, and consider transfer to an ICU.[16] However, studies analyzing qSOFA as a bedside screening tool have contradictory results, and most have demonstrated a low sensitivity for detecting sepsis.[31–34] For example, performance characteristics for the qSOFA in 82 validated maternal sepsis cases demonstrated a sensitivity of only 50%.[34] Moreover, none of these tools have been validated for pregnancy.

Multiple pregnancy-specific tools are available for identifying early warning signs of sepsis (eg, Modified Early Obstetric Warning System [MEOWS],[35] Sepsis in Obstetrics Score [SOS],[36] quick SOFA modified for pregnancy [qSOFA-P],[37] the California Maternal Quality Care Collaborative [CMQCC] 2-step process,[38] Maternal Early Warning Trigger [MEWT],[39] and the obstetric-modified qSOFA [omqSOFA])[40] but each has significant limitations as a single screening tool.

In addition, there have been other attempts to devise a one-step pregnancy-specific scoring system to predict ICU admission in maternal sepsis. Evaluation of the SOS, a combination of maternal temperature, blood pressure, heart rate, respiratory rate, peripheral oxygen saturation, white blood cell count, and lactic acid level modified to account for normal physiological changes of pregnancy, reported a positive predictive value of only 16.7% for ICU admission in an initial retrospective study.[36] A prospective validation study of the SOS found that a score of $\geq$6 had a sensitivity of 64%, specificity of 88%, positive predictive value of 15%, and negative predictive value of 98.6% for ICU admission, and was independently associated with positive blood cultures and fetal tachycardia.[41]

The CMQCC has a 2-step screening and confirmation process currently undergoing validation (Figure 1).[38] Step 1 assigns 1 point for each abnormal vital sign parameter, which includes maternal temperature $<$36°C (96.8°F) or $\geq$38°C (100.4°F), heart rate $>$100 bpm and sustained for 15 minutes, respiratory rate $>$24 breaths per minute and sustained for 15 minutes, and a white blood cell count $>$15,000 mm^3 or $<$4000 mm^3 or $>$10% immature neutrophils. A threshold of $\geq$2 points is considered positive. If the step-1 screen is positive, step 2 involves confirmation of organ dysfunction by combining clinical evaluation at the bedside and laboratory assessment. Based on clinical practice data sets, the anticipated performance of the 2-step process is estimated to have a sensitivity of 97% and a specificity of 99%. However, because there are limited data on the validation of the CMQCC 2-step process, there remain concerns that a high screen-positive rate at step 1 may pose challenges related to alarm fatigue, resource utilization, and the costs associated with adopting this process.

Although the best early warning system to detect sepsis in pregnant and postpartum patients has not been clearly defined, important principles are that: (1) the implementation of an early warning system may decrease maternal risk,[35,42] and (2) clinicians should avoid the use of a single screening tool and understand the limitations of the screening tools in use. **We recommend that institutions develop their own procedures and protocols for the detection of maternal sepsis, avoiding the use of a single screening tool alone (GRADE 1B).**[17]

What is the initial management of maternal sepsis?

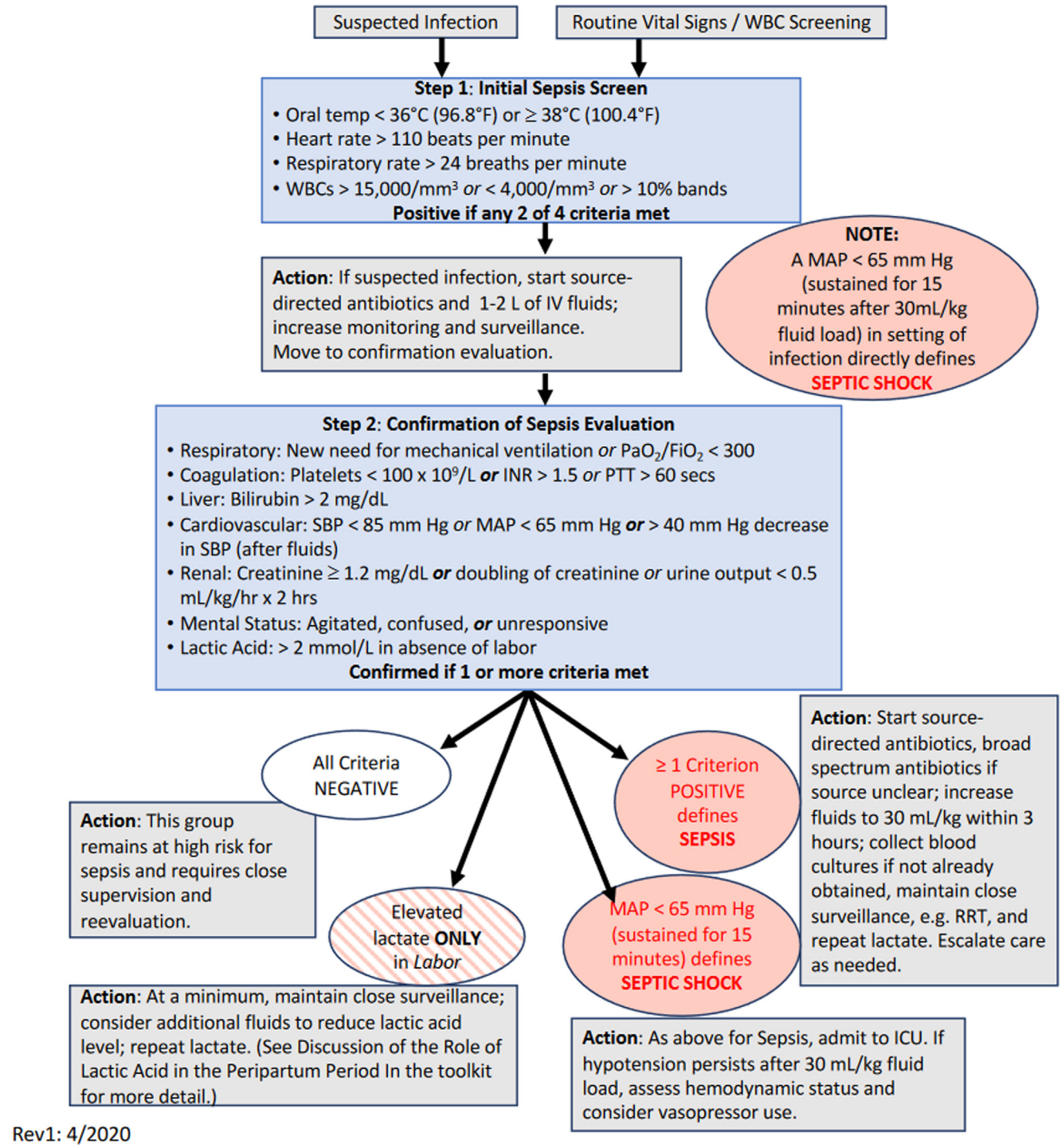
Initial management of maternal sepsis is illustrated in Figure 2. Organ dysfunction in a previously healthy person should raise suspicion of sepsis. If the history or physical examination supports a possible diagnosis of sepsis *without shock*, a rapid assessment for infectious vs noninfectious causes of acute illness is recommended.[17] This rapid assessment should occur within 3 hours and, in addition to history and clinical examination, should include tests for both infectious and noninfectious causes and immediate treatment for conditions that can mimic sepsis (eg, diabetic ketoacidosis, adrenal crises, pancreatitis, anaphylaxis, cardiomyopathy, etc.). If the history and physical examination support sepsis *with shock*, the assessment should occur more rapidly, within 1 hour. Laboratory evaluation commonly includes a complete blood count with differential, cultures (blood, sputum, urine, and others as clinically indicated), serum lactate levels, a comprehensive metabolic panel that includes renal and hepatic function, coagulation studies with international normalized ratio, and arterial blood gas and peripheral blood smear, where available. **We recommend obtaining tests to evaluate for infectious and noninfectious causes of life-threatening organ dysfunction in pregnant and postpartum patients with possible sepsis (Best Practice). We recommend that an evaluation for infectious causes in pregnant or postpartum patients in whom sepsis is suspected or identified include appropriate microbiologic cultures, including blood, before starting antimicrobial therapy as long as there are no substantial delays in timely administration of antibiotics (Best Practice).**[15]

Procalcitonin is a biomarker of response to infection that has been used to individualize antibiotic therapy. However, procalcitonin-guided protocols do not consistently decrease mortality, or ICU and hospital length of stay.[43] Currently, there is no role for procalcitonin-guided protocols for antibiotic initiation in pregnant or postpartum patients.[17]

Although lactate levels $>$2 mmol/L suggest possible sepsis,[16,44] intrapartum lactate elevations of $>$2 mmol/L are typical. Some healthy patients, especially in later stages of labor, have normal values $>$4 mmol/L; thus, these values should be interpreted cautiously during labor.[45,46] **We recommend obtaining a serum lactate level in pregnant or postpartum patients in whom sepsis is suspected or identified (GRADE 1B).**[17]

Molecular techniques have improved the ability to identify inciting organisms not detected by culture-based methods. Peptide nucleic acid fluorescence in situ hybridization stains, matrix-assisted laser desorption-ionization/time-of-flight mass spectroscopy, and polymerase chain

FIGURE 1
California Maternal Quality Care Collaborative 2-step system for diagnosis of maternal sepsis[38]



FiO_2, fraction of inspired oxygen; *ICU*, intensive care unit; *INR*, international normalized ratio; *IV*, intravenous; *MAP*, mean arterial pressure; *PaO_2*, partial pressure of oxygen; *PTT*, partial thromboplastin time; *RRT*, rapid response team; *SBP*, systolic blood pressure; *WBC*, white blood cell.

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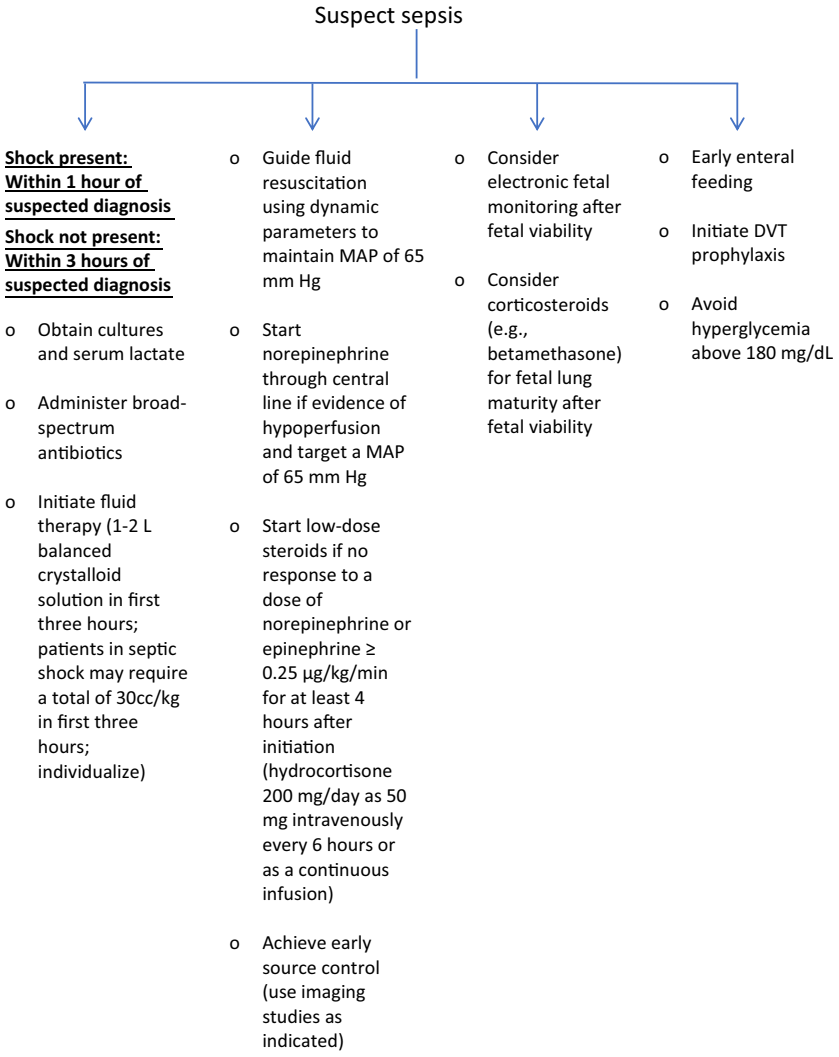
FIGURE 2
Initial treatment of sepsis during pregnancy



DVT, deep venous thrombosis; *MAP*, mean arterial pressure.

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reaction–based systems are commercially available and can provide pathogen identification from blood samples before cultures become positive.[47] Polymerase chain reaction testing results are positive in approximately 11% of patients with a clinical suspicion of bacteremia but negative blood cultures.[48]

Early administration of appropriate antimicrobials is a crucial intervention to reduce mortality in patients with sepsis. These data are most compelling in patients presenting with septic shock[49]; therefore, the SSC guidelines strongly recommend *immediate* administration of antibiotics in patients with potential septic shock.[17] The importance of early antibiotic administration in maternal sepsis cannot be overemphasized. In a review of 82 maternal sepsis cases during delivery hospitalization, the mortality rate for those who received antibiotics within 1 hour of diagnosis was 8.3%, as opposed to 20% for the patients who received antibiotics after >1 hour.[34] **In pregnant or postpartum patients with septic shock or a high likelihood of sepsis, we recommend administration of empiric broad-spectrum antimicrobial therapy, ideally within 1 hour of recognition (GRADE 1C).** The presumed source, likely microorganisms, and local patterns of antibiotic resistance will drive empiric antibiotic choices. Because infections leading to maternal sepsis are frequently polymicrobial, initial antimicrobial selection should cover both anaerobic and aerobic gram-positive and gram-negative bacteria. In pregnant or postpartum patients with sepsis or septic shock who are at high risk for methicillin-resistant *Staphylococcus aureus* (MRSA), the use of broad-spectrum agents with activity against MRSA

activity is recommended. If patients are at high risk for multidrug resistance, the use of 2 antimicrobials with gram-negative coverage over 1 gram-negative antimicrobial is recommended. Recommendations for empiric coverage are expected to change as antibiotic resistance spreads. Hospitals may have specific recommendations in place, or guidance may be sought from a consultant in infectious disease or specialty society guidelines.

The most current SSC guidelines[17] recommend prolonged infusion of beta-lactams for maintenance after an initial bolus over conventional bolus infusions (≤30 minutes) because prolonged infusion has been shown to reduce short-term mortality in sepsis and septic shock.[50,51] Although it has long been known that the pharmacokinetics of beta-lactam antibiotics are altered during pregnancy because of their faster elimination and lowered plasma concentrations, prolonged infusions of beta-lactams have not been well studied in treating maternal sepsis. It is best practice to optimize dosing strategies of antimicrobials on the basis of acceptable pharmacokinetic/pharmacodynamic principles and specific drug properties. Where available, guidance can be sought from infectious disease consultants or clinical pharmacists.

Antimicrobial stewardship is important in caring for a pregnant or postpartum patient with sepsis or septic shock. Although the optimal duration of therapy is unknown, randomized trials on a shorter vs longer course of therapy in nonobstetrical patients with different infections, such as urinary tract infections and bacteremia, have demonstrated that shorter courses of therapy are as effective as longer courses with less adverse side effects.[52–54] However, very few of these trials focused only on critically ill patients with sepsis or septic shock. Given the benefit of a shorter duration of antimicrobials in other infectious conditions, the most current SSC guidelines suggest daily evaluation for the deescalation of antimicrobials.[17] Broad-spectrum antibiotic coverage should be narrowed and focused once a pathogen is identified or there is clinical improvement. Table 4 summarizes some options for empiric antibiotic coverage for common infections that occur during pregnancy.

After antibiotics are initiated and cultures obtained for a suspected case of sepsis, a search should begin for a focus of infection amenable to source control. Imaging is often required. If a specific focus is identified, appropriate steps should be undertaken, such as curettage for retained products of conception or drainage of an abscess. If the source of infection is suspected to be from an intravascular access device, prompt removal of the device is recommended after alternative access is established.[17] The most effective intervention with the least potential for physiological derangement should be used (eg, percutaneous drainage is preferable to more extensive surgery).[15] The exception to this rule are necrotizing soft-tissue infections, in which extensive debridement is required, including hysterectomy in cases of suspected or confirmed myometrial infection or necrosis. **After a diagnosis of sepsis in pregnancy is made, we recommend rapid identification or exclusion of an anatomic source of infection and emergency source control when indicated (Best Practice).**

What is the role of fluid therapy in the management of maternal sepsis?

Fluid resuscitation should be part of the initial intervention if hypotension or hypoperfusion is present. Fever, venodilation,

TABLE 4
Proposed broad-spectrum empiric antibiotic coverage in sepsis complicating pregnancy

Source infection	Recommended antibiotics
Community-acquired pneumonia	Cefotaxime, ceftriaxone, ertapenem, or ampicillin plus azithromycin, clarithromycin, or erythromycin.[55]
Hospital-acquired pneumonia	Low-risk patients may be treated with ceftriaxone, ampicillin-sulbactam, ertapenem, meropenem, imipenem, or cefepime. Patients at high risk of mortality may need double coverage for *Pseudomonas* (beta lactam plus an aminoglycoside or a quinolone) and MRSA coverage with vancomycin or linezolid.[56,57]
Chorioamnionitis	Ampicillin plus gentamicin.[58] Add anaerobic coverage with clindamycin or metronidazole if cesarean delivery required.
Endomyometritis	Ampicillin, gentamicin, and metronidazole (or clindamycin). Alternatively, may use cefotaxime or ceftriaxone plus metronidazole.[59]
Urinary tract infections	Gentamicin with ampicillin Alternatively, may use monotherapy with a carbapenem or piperacillin-tazobactam.[60]
Abdominal infections	Ceftriaxone, cefotaxime, ceftazidime, or cefepime plus metronidazole.[61] Complicated cases may require monotherapy with a carbapenem or piperacillin-tazobactam.
Skin and soft tissues (necrotizing)	Vancomycin plus piperacillin-tazobactam.[62] If group A *Streptococcus* or *Clostridium perfringens* are present, use penicillin G plus clindamycin.

MRSA, methicillin-resistant Staphylococcus aureus.

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and capillary leakage all lead to inadequate preload in sepsis patients. The 2021 SSC guidelines recommend that at least 30 mL/kg of fluids be given in the first 3 hours,[17] but this recommendation may be overly aggressive in pregnancy, in which colloid oncotic pressure is lower and the risk of pulmonary edema is higher. Only approximately 50% of hypotensive septic patients are fluid responders. In those who are not, aggressive fluid administration may produce third-spacing, leading to left ventricular diastolic dysfunction from ventricular wall edema, as well as pulmonary edema, cerebral edema, bowel edema with increased intraabdominal pressure, and higher mortality.[63] Therefore, a more restrictive approach to initial fluid resuscitation may be necessary in pregnant patients with suspected sepsis or septic shock. **We recommend early intravenous administration (within the first 3 hours) of 1 to 2 L of balanced crystalloid solutions in sepsis complicated by hypotension or suspected organ hypoperfusion (GRADE 1C).**

The type of fluid therapy used for resuscitation in sepsis and septic shock has been studied in nonpregnant patients. On the basis of the best available evidence, balanced crystalloid solutions (eg, Lactated Ringer's, Plasma-Lyte) are recommended over chloride-rich solutions (eg, 0.9% saline)[64,65]; however, more robust experimental trials are ongoing. Albumin can be considered in patients who receive a large volume of crystalloids, but a cutoff for crystalloids above which albumin might be considered has not been established. **We recommend the use of a balanced crystalloid solution as a first-line fluid for resuscitation in pregnant and postpartum patients with sepsis or septic shock (GRADE 1B).**[17] Hydroxyethyl starch and gelatin have been associated with increased risk of acute kidney injury and mortality,[66] and are not recommended. **We recommend against the use of starches or gelatin for resuscitation in pregnant and postpartum patients with sepsis or septic shock (GRADE 1A).**[17]

After the initial fluid resuscitation, an ongoing, detailed evaluation of the patient's response to fluid resuscitation is recommended. Static measures of preload (eg, central venous pressure or pulmonary artery occlusion pressure) are poor predictors of fluid responsiveness and should not be used to guide fluid therapy.[67] In contrast, dynamic measures used to guide fluid resuscitation have been shown to reduce mortality, ICU stay length, and mechanical ventilation duration in nonobstetrical patients.[68] The latter may be accomplished using pulse-pressure variation, passive leg raising, or echocardiography, where available.

In a mechanically ventilated patient with an arterial line, pulse-pressure variation may be used as an alternative way to assess fluid responsiveness. Determination of pulse-pressure variation is accomplished by analyzing the waveform of an arterial line, which should not be affected by pregnancy. However, this metric is reliable only in sedated individuals receiving positive pressure, controlled mechanical ventilation, and those in sinus rhythm.[69] If the pulse pressure varies by >13% with the respiratory cycle, the patient is volume-responsive.

In patients who are breathing spontaneously or are not in sinus rhythm, a rapid and reversible test of fluid responsiveness can be performed with passive leg raising to 30° to 45°, which causes an autotransfusion of close to 300 mL of blood from the legs into the chest. After 2 to 3 minutes of passive leg raising, fluid responders will have an increase in cardiac output (using noninvasive cardiac output monitors where available), whereas those who do not improve are probably better treated with vasopressors.[70] Assessing cardiac output through noninvasive cardiac monitors after passive leg raising in the third trimester may not be useful because of uterine compression of the inferior vena cava.[71] Another alternative measure to identify fluid responsiveness in this situation includes administering a small bolus of fluid (250–500 mL) and measuring the cardiac output. If the cardiac output increases after such an intervention, further fluid administration is likely indicated.

Point-of-care ultrasound has also been used to identify fluid responsiveness by measuring the diameter of the inferior vena cava with respiration, determining stroke volume variation, and assessing the hemodynamic response of the carotid artery to autotransfusion. Inferior vena cava diameter <1.5 cm with significant variation in caliber with the respiratory cycle predicts fluid responsiveness, whereas a diameter >2 to 2.5 cm with minimal variability with the respiratory cycle suggests that the patient is already fully fluid-loaded. Measurement of stroke volume variation in response to changes in intrathoracic pressure allows estimation of preload and prediction of cardiac index changes in response to fluid loading.[72] In a study of 33 women after 35 weeks of gestation, the hemodynamic response of the carotid artery to autotransfusion after passive leg raise was significantly greater in women with narrow vs normal pulse pressure. Therefore, pulse pressure correlates with the physiological response to autotransfusion and provides a qualitative indication of intravascular volume in the third trimester of pregnancy.[73] However, these ultrasound techniques have limited application in low-resource settings. In these settings, alternative measures such as normalization of skin temperature (normal range, 37.0°C±0.5°C)[74] and capillary refill time (normal time, ≤2 seconds) or diminution of skin mottling, are reproducible signs of tissue reperfusion in nonobstetrical patients.[75,76] **We recommend ongoing, detailed evaluation of the patient's response to fluid resuscitation guided by dynamic measures of preload (GRADE 1B).**[17]

The 2021 SSC guidelines suggest the use of pulmonary-artery catheters (PACs) over noninvasive monitoring in patients with septic shock.[17] However, this technique is highly invasive, has substantial procedure-related risks, and requires specific expertise in interpretation of the thermodilution curves, which may not be as reliable in pregnancy.[77] Therefore, PACs should be used in cases of maternal sepsis only in very specific clinical situations when less or minimally invasive options are not available.[77]

The 2021 SSC guidelines support the use of resuscitative strategies to reduce serum lactate levels to guide fluid

resuscitation in patients with sepsis and septic shock; however, the guidelines highlight that these levels should be interpreted while considering the clinical context and other causes of elevated lactate, such as normal intrapartum elevations.[17]

When are vasopressors and inotropes indicated in maternal sepsis?

In hypotensive patients who are not fluid-responsive or not candidates for further fluid resuscitation (eg, patients with pulmonary edema), vasopressors and inotropes are used to increase blood pressure and cardiac contractility, respectively. The purpose of vasopressors is to constrict the pathologically dilated systemic circulation and maintain adequate perfusion (Table 5).

Guidelines recommend norepinephrine as the first-line agent with an initial target MAP of 65 mm Hg, although this threshold has not been studied in pregnant people.[17] Determining the target MAP in a pregnant patient with sepsis must be individualized and consider overall organ perfusion. Lower blood pressure targets may be acceptable during pregnancy, provided that no signs of hypoperfusion are present (eg, altered mental status, oliguria, elevated serum lactate, cold extremities, or evidence of fetal compromise). Early goal-directed therapy involving manipulation of cardiac preload, afterload, and contractility to achieve a balance between systematic oxygen delivery and oxygen demand is no longer recommended in the management of sepsis.[82–84]

In a meta-analysis of 11 randomized trials, norepinephrine resulted in lower mortality and lower risk of arrhythmias compared with dopamine.[79] Norepinephrine has been studied in human pregnancy and is often used to maintain blood pressure with regional anesthesia at the time of cesarean delivery.[85] Acknowledging the lack of high-quality evidence in the setting of pregnancy-associated septic shock, norepinephrine nevertheless seems to be a reasonable first-line vasopressor, especially at low doses. **We recommend the use of norepinephrine as the first-line vasopressor during pregnancy and the postpartum period with septic shock (GRADE 1C).**

The evidence regarding the use of other vasopressors is more limited, and a theoretical interaction of vasopressin with oxytocin receptors has been hypothesized.[86] Despite these theoretical concerns, vasopressin remains a reasonable second-line agent after norepinephrine for refractory shock with fetal monitoring indicated after viability. In the setting of myocardial dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, dobutamine can be added to norepinephrine, or epinephrine used alone.[17] Because of a lack of proven benefit, levosimendan, a calcium-sensitizing drug with inotropic and vasodilatory properties, is not recommended in the management of septic shock. Figure 3 depicts a

TABLE 5
Common vasopressors and inotropes used to treat septic shock during pregnancy and the postpartum period[78]

Vasopressor/ inotrope	Mechanism of action	Effects	Comments
Norepinephrine	Potent alpha-1 and beta-1 adrenergic receptor agonist	Increases the mean arterial pressure with a minimal impact on heart rate	• Lower mortality and lower risk of arrhythmias vs dopamine[79] • First-line agent for septic shock[15]
Vasopressin	Endogenous peptide hormone produced by the hypothalamus and stored and released by the posterior pituitary gland	Vasoconstrictive activity through binding of V_1receptors on vascular smooth muscle resulting in increased arterial blood pressure	• Higher doses associated with cardiac, digital, and splanchnic ischemia[80] • Theoretical interaction with oxytocin receptors has been hypothesized[43]
Epinephrine	Potent β-1 adrenergic activity and moderate β-2 and α-1 adrenergic receptor activity	Lower doses (action on β-1 adrenergic receptors): • increase CO • decrease SVR • variable effects on MAPHigher doses: increase SVR and CO	• May be used alone in patients with septic shock and myocardial dysfunction[15] • Potential adverse effects include arrhythmias and impaired splanchnic circulation[79,81] • May increase aerobic lactate production via stimulation of skeletal muscle β-2 adrenergic receptors, making the use of serum lactate to guide resuscitation challenging[17]
Dobutamine	Inotrope that stimulates β-1 receptors of the heart	• Increases CO output and oxygen transport • Increases tissue performance • Improves acidosis and hyperlactatemia	Add to norepinephrine for patients with myocardial dysfunction who persist in septic shock[15]

CO, cardiac output; *MAP*, mean arterial pressure; *SVR*, systemic vascular resistance.
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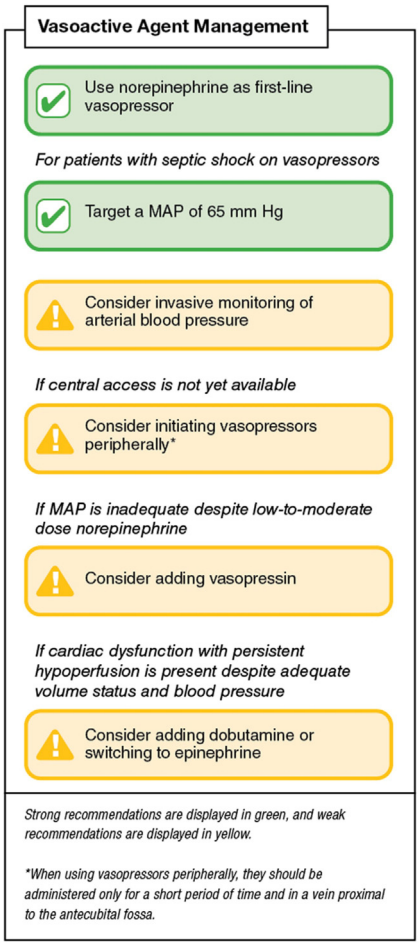
FIGURE 3
Summary of vasoactive agents for sepsis[17]



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MAP, mean arterial pressure.
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practical approach to the general use of vasoactive agents in septic shock, which is also a reasonable approach in pregnant and postpartum patients in septic shock.

Are there additional therapies that may benefit a pregnant or postpartum patient with septic shock?

In nonpregnant patients in whom hemodynamic stability cannot be achieved with the use of vasoconstrictors, hydrocortisone is recommended because of the possibility of sepsis-induced adrenal failure.[17] Systemic corticosteroids may accelerate resolution of shock.[87] A typical corticosteroid regimen for adults in septic shock is intravenous (IV) hydrocortisone 200 mg/d (50 mg every 6 hours or as a continuous infusion) for 7 days. The guidelines suggest that corticosteroids be started in patients with an ongoing requirement for vasopressor therapy. Ongoing requirement is defined as a dose of norepinephrine or epinephrine $\geq$0.25 μg/kg/min for at least 4 hours after initiation to maintain the target MAP.[17] **We suggest using IV corticosteroids in pregnant or postpartum patients with septic shock who continue to require vasopressor therapy (GRADE 2B).**

Other therapies with recommendations extrapolated from the general population may be considered for the pregnant patient with septic shock, although data are limited for use during pregnancy. Stress ulcer prophylaxis is recommended for patients in septic shock with risk factors for gastrointestinal bleeding (eg, use of anticoagulant or nonsteroidal antiinflammatory medications, chronic vomiting, etc.). Given that common medications to prevent peptic ulcer disease are safe to use in pregnancy, such therapy is reasonable for pregnant patients with septic shock and risk factors for gastrointestinal bleeding.

The risk of venous thromboembolism (VTE) has been reported to be as high as 37% in patients with sepsis.[88] Low-molecular-weight heparin (LMWH) is preferred over unfractionated heparin to reduce the risk of VTE because it has a better safety profile.[89] However, unfractionated heparin may be preferred in specific clinical circumstances (eg, allergy to LMWH, imminent delivery, etc.). Although the incidence of VTE in pregnant patients with sepsis and septic shock is unknown, medical comorbidities and immobilization in pregnancy are known risk factors for VTE in pregnancy.[90] **Because of an increased risk of VTE in sepsis and septic shock, we recommend the use of pharmacologic VTE prophylaxis in pregnant and postpartum patients in septic shock (GRADE 1B).**[17]

Hyperglycemia, defined as a glucose value >180 mg/dL in the general population, is associated with increased mortality in critically ill patients,[91–93] although pregnancy-specific data are lacking. **We suggest initiating insulin therapy at a glucose level >180 mg/dL in critically ill pregnant patients with sepsis (GRADE 2C).**[17]

Therapies that have shown no or inconsistent benefit in various trials of nonobstetrical patients with sepsis include the use of polymyxin B hemoperfusion or other blood purification techniques, IV immunoglobulins, IV vitamin C, and sodium bicarbonate therapy with lactic acidemia. There is little to no evidence regarding these therapies in pregnant and postpartum patients with septic shock; thus, they are not recommended.

When is delivery indicated in a pregnant patient with sepsis?

The presence of sepsis alone is not an immediate indication for delivery (except in cases of intraamniotic infection).[94] The decision to deliver the fetus should be individualized and depends on gestational age and maternal and fetal conditions. The primary objective should be hemodynamic supportive therapy for maternal benefit and antimicrobial treatment with appropriate infection source control.[17,95,96] The involvement of neonatology, anesthesiology, and critical care consultants is essential.[40] In most cases, resuscitation that improves maternal hemodynamics will result in

improved uteroplacental perfusion and improved fetal condition.[97] After initial stabilization of the pregnant patient with sepsis, fetal monitoring is recommended. At the limit of fetal viability, the team should incorporate informed patient or family preferences into decision-making on fetal monitoring, if possible. Delivery should be reserved for the usual obstetrical indications. However, in cases where a uterine infection is suspected or confirmed to be the source of sepsis (eg, intraamniotic infection), delivery is the appropriate source control measure.[40,94,97] **If a uterine source for sepsis is suspected or confirmed, we recommend prompt delivery or evacuation of uterine contents to achieve source control, regardless of gestational age (GRADE 1C).**

Corticosteroids for fetal lung maturity are not contraindicated and may be used in sepsis if indicated[98] (regardless of use of hydrocortisone for refractory septic shock). Key interventions in the treatment of sepsis are depicted in Figure 2.

What are the maternal and perinatal outcomes associated with sepsis?

Despite maternal sepsis being a leading cause of pregnancy-related deaths, the mortality rate of sepsis in pregnant people is difficult to quantify. The few existing studies have reported rates between 1.4% and 7.7%.[13,25,99] The fatality rate is lower when H1N1 influenza, which has a high case fatality rate, is excluded. In the general population, actual case fatality rates of sepsis have decreased over time: the highest estimate was a case fatality rate of 35% in 2004, which fell to 25% in 2009, whereas the lowest estimate was 18% in 2004, declining to 14% in 2009.[100] However, both the incidence and mortality of sepsis depend on age, making it difficult to find an appropriate comparison group for reproductive-age people capable of pregnancy.

An analysis from New Zealand and Australia of all adults with severe sepsis admitted to an ICU between 2000 and 2012 included a breakdown of young adults (age $\leq$44 years; mean age 31.6 years). For this group, average in-hospital mortality was 12%, and 8% in the absence of comorbidities. Like US figures, mortality in this age group of Australians and New Zealanders with severe sepsis decreased significantly over time, from 22% in 2000 to 7% in 2012.[101]

In the United States, sepsis is also a leading cause of severe maternal morbidity. It is estimated that 50 patients experience life-threatening morbidity from sepsis for each maternal death.[102,103] Common morbidities in adult survivors of sepsis include organ dysfunction, amputations, depression and anxiety, loss of self-esteem and self-belief, insomnia, panic attacks, nightmares, disabling muscle and joint pains, and decreased cognitive function.[104,105] Infertility may result from a sepsis-related pelvic infection or a hysterectomy performed for source control, and is a unique and consequential morbidity in some survivors of maternal sepsis.[105,106]

It is important to note that survival to hospital discharge does not guarantee a normal outcome or quality of life; in the United States, only 20% of patients with severe sepsis were discharged to home, whereas 35% were discharged to a skilled nursing facility and 12% to some type of home care.[5] Without data specific to pregnancy, it is unknown what proportion of pregnant or postpartum sepsis survivors require assisted recovery. However, several best practices for discharge planning in adult sepsis survivors are reasonable to consider in pregnant patients with sepsis and septic shock. These include screening for economic and social support and coordinating referrals to meet these needs; providing information about postintensive care syndrome (PICS) with specific details about the ICU stay, sepsis and related diagnoses and treatments, and common impairments after sepsis; assessment and follow-up for physical, cognitive, and emotional problems; and consideration of a posthospital rehabilitation program for any pregnant patient receiving mechanical ventilation for $>$48 hours or an ICU stay of $>$72 hours.[17] **Because of an increased risk of physical, cognitive, and emotional problems in survivors of sepsis and septic shock, we recommend ongoing comprehensive support for pregnant and postpartum sepsis survivors and their families (Best Practice).**

Preterm delivery is common after critical maternal illness, including sepsis, even when the source is not uterine. This finding is consistent with the pathophysiology of sepsis, in which inflammatory mediators are released systemically.[107] In a series from Ireland reporting on pregnant and postpartum women with bacteremia, the preterm birth rate was 16.8%, nearly 3 times the rate found in the control groups at the same institutions.[10] This rate included patients diagnosed with bacteremia antepartum, intrapartum, and postpartum. In patients with antepartum bacteremia, 69% either miscarried or delivered preterm. Those with bacteremia of uterine origin had the highest rates of preterm birth, as expected given that this is a contraindication to pregnancy continuation. Among patients with a nonpelvic source of bacteremia in the antepartum period, 12% miscarried, 33% delivered soon after onset, and the remainder delivered between 1 week and 7 months after onset. Bacteremia during pregnancy was associated with a 29% risk of preterm delivery in a French study, with an overall fetal mortality rate of 10%; when maternal bacteremia occurred during the second trimester, the fetal death rate was 40%.[108] In a small study focused specifically on *E coli* bacteremia during pregnancy, the same researchers determined that the rate of fetal death was 27% overall, despite adequate antibiotic therapy.[109]

More recently, a retrospective cohort study at a single referral center analyzed perinatal outcomes among patients with antepartum sepsis who did not deliver during their infection hospitalization.[110] Patients with antepartum sepsis had increased odds of placental dysfunction

Summary of recommendations

Number	Recommendation	GRADE
1	We recommend that clinicians consider the diagnosis of sepsis in pregnant or postpartum patients with otherwise unexplained end-organ damage in the presence of a suspected or confirmed infectious process, regardless of the presence of fever.	1C
2	We recommend that sepsis and septic shock in pregnancy be considered medical emergencies and that treatment and resuscitation begin immediately.	Best Practice
3	We recommend that hospitals and health systems use a performance improvement program for sepsis in pregnancy with sepsis screening tools and metrics.	1B
4	We recommend that institutions develop their own procedures and protocols for the detection of maternal sepsis, avoiding the use of a single screening tool alone.	1B
5	We recommend obtaining tests to evaluate for infectious and noninfectious causes of life-threatening organ dysfunction in pregnant and postpartum patients with possible sepsis.	Best Practice
6	We recommend that an evaluation for infectious causes in pregnant or postpartum patients in whom sepsis is suspected or identified include appropriate microbiologic cultures, including blood, before starting antimicrobial therapy, as long as there are no substantial delays in starting antibiotics.	Best Practice
7	We recommend obtaining a serum lactate level in pregnant or postpartum patients in whom sepsis is suspected or identified.	1B
8	In pregnant or postpartum patients with septic shock or a high likelihood of sepsis, we recommend administration of empiric broad-spectrum antimicrobial therapy, ideally within 1 h of recognition.	1C
9	After a diagnosis of sepsis in pregnancy is made, we recommend rapid identification or exclusion of an anatomic source of infection and emergency source control when indicated.	Best Practice
10	We recommend early intravenous administration (within the first 3 h) of 1 to 2 L of balanced crystalloid solutions in sepsis complicated by hypotension or suspected organ hypoperfusion.	1C
11	We recommend the use of a balanced crystalloid solution as a first-line fluid for resuscitation in pregnant and postpartum patients with sepsis or septic shock.	1B
12	We recommend against the use of starches or gelatin for resuscitation in pregnant and postpartum patients with sepsis or septic shock.	1A
13	We recommend ongoing, detailed evaluation of the patient's response to fluid resuscitation guided by dynamic measures of preload.	1B
14	We recommend the use of norepinephrine as the first-line vasopressor during pregnancy and the postpartum period with septic shock.	1C
15	We suggest using intravenous corticosteroids in pregnant or postpartum patients with septic shock who continue to require vasopressor therapy.	2B
16	Because of an increased risk of VTE in sepsis and septic shock, we recommend the use of pharmacologic VTE prophylaxis in pregnant and postpartum patients in septic shock.	1B
17	We suggest initiating insulin therapy at a glucose level >180 mg/dL in critically ill pregnant patients with sepsis.	2C
18	If a uterine source for sepsis is suspected or confirmed, we recommend prompt delivery or evacuation of uterine contents to achieve source control, regardless of gestational age.	1C
19	Because of an increased risk of physical, cognitive, and emotional problems in survivors of sepsis and septic shock, we recommend ongoing comprehensive support for pregnant and postpartum sepsis survivors and their families.	Best Practice

VTE, venous thromboembolism.

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compared with those without sepsis (35.6% vs 23.8%; OR, 1.77; 95% CI, 1.04–3.02), and antepartum sepsis was an independent factor for placental dysfunction after adjusting for possible confounders (adjusted OR, 1.88; 95% CI, 1.10–3.23). More robust data are necessary to confirm this association.

How can deaths from maternal sepsis be prevented?

Among the studies of sepsis-related maternal mortality, some clear patterns emerge. Among pregnant people who died from sepsis, most had a delay in care and a delay in the escalation of care.[34] Most were afebrile, possibly delaying the

Society for Maternal-Fetal Medicine Grading System: GRADE (Grading of Recommendations Assessment, Development, and Evaluation) Recommendations[111,a]

Grade of recommendation	Clarity of risk and benefit	Quality of supporting evidence	Implications
1A. Strong recommendation, high-quality evidence	Benefits clearly outweigh risks and burdens, or vice versa.	Consistent evidence from well-performed, randomized controlled trials, or overwhelming evidence of some other form. Further research is unlikely to change confidence in the estimate of benefit and risk.	Strong recommendation that can apply to most patients in most circumstances without reservation. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
1B. Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risks and burdens, or vice versa.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on confidence in the estimate of benefit and risk and may change the estimate.	Strong recommendation that applies to most patients. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
1C. Strong recommendation, low-quality evidence	Benefits seem to outweigh risks and burdens, or vice versa.	Evidence from observational studies, unsystematic clinical experience, or randomized controlled trials with serious flaws. Any estimate of effect is uncertain.	Strong recommendation that applies to most patients. Some of the evidence base supporting the recommendation is, however, of low quality.
2A. Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burdens.	Consistent evidence from well-performed randomized controlled trials or overwhelming evidence of some other form. Further research is unlikely to change confidence in the estimate of benefit and risk.	Weak recommendation; best action may differ depending on circumstances or patients or societal values.
2B. Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burdens; some uncertainty in the estimates of benefits, risks, and burdens.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to influence confidence in the estimate of benefit and risk and may change the estimate.	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances.
2C. Weak recommendation, low-quality evidence	Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens.	Evidence from observational studies, unsystematic clinical experience, or randomized controlled trials with serious flaws. Any estimate of effect is uncertain.	Very weak recommendation, other alternatives may be equally reasonable.
Best Practice	Recommendation in which either: (1) there is an enormous amount of indirect evidence that clearly justifies strong recommendation (direct evidence would be challenging, and inefficient use of time and resources, to bring together and carefully summarize), or (2) recommendation to the contrary would be unethical.		

[a] Adapted from Guyatt et al.[112]

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Guidelines

The content of this document reflects the national and international guidelines related to sepsis

Organization	Title	Year of publication
American College of Obstetricians and Gynecologists, Society for Maternal-Fetal Medicine	Practice Advisory: Use of Antenatal Corticosteroids at 22 Weeks of Gestation[98]	2021
Sepsis-3 Taskforce	The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) 2016[16]	2016
Society of Obstetric Medicine of Australia and New Zealand	SOMANZ Guidelines for the Investigation and Management of Sepsis in Pregnancy[40]	2017
Surviving Sepsis Campaign	International Guidelines for Management of Sepsis and Septic Shock[15]	2016
Surviving Sepsis Campaign	International Guidelines for Management of Sepsis and Septic Shock[17]	2021
World Health Organization	Statement on Maternal Sepsis[19]	2017

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recognition of the presence of sepsis.[28] Even after diagnosis, 73% of patients were started on antibiotics that provided inadequate coverage.[28] The SSC guidelines[17] can encourage the implementation of care bundles to facilitate early recognition of sepsis through performance improvement programs and early involvement of consultants with expertise in infectious disease to expedite the treatment of sepsis and help improve outcomes. Fostering mutual trust and respect with patients early in their pregnancy, empowering them to speak up about urgent maternal warning signs, actively listening to their concerns, and addressing structural racism and personal biases are essential steps toward reducing delays in care and maternal mortality from sepsis.[29]

How can hospitals identify system and process opportunities for improvement in maternal sepsis diagnosis and management?

Multidisciplinary reviews for systems improvement should be conducted for maternal sepsis cases to assess the screening program, the quality of care provided to the patient, and whether instances of bias may have affected care. Multidisciplinary case review should: (1) identify all maternal sepsis cases; (2) determine adherence to maternal sepsis response protocols; (3) determine whether instances of bias may have affected care (ie, race, ethnicity, socioeconomic status, insurance status, history of substance use, etc.); and (4) identify and implement ways to make system improvements. Process mapping may assist in identifying systemic gaps, identifying trends and opportunities, implementing interventions to address them, and measuring improvements. Collaboration with referral hospitals or state maternal mortality review committees can aid smaller hospitals that face barriers to conducting their own multidisciplinary reviews. In hospitals with ICUs where the intensivist is the admitting medical officer (ie, "closed" ICUs), policies should be in place that define the collaborative role between the intensivist and maternal–fetal medicine subspecialist to care for these complex patients.

Conclusion

Sepsis continues to be a major cause of morbidity and mortality worldwide. Treatment during pregnancy should follow the same basic principles as in the nonpregnant population, including early recognition, fluid therapy, timely broad-spectrum antibiotics, and source control. Vasopressors, such as norepinephrine, should be used when indicated during pregnancy. In most cases, delivery should be guided by obstetrical indications. In pregnancy, sepsis (particularly septic shock) is associated with an increased risk for preterm delivery, prolonged recovery, stillbirth, and maternal death.

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