Sepsis in pregnancy and the puerperium

C.E.G. Burlinson, a D. Sirounis, b,c K.R. Walley, b,d A. Chau a,c

a Department of Anesthesia, British Columbia Women’s Hospital, Vancouver, BC, Canada
b Division of Critical Care Medicine, Department of Medicine, St. Paul’s Hospital, Vancouver, BC, Canada
c Department of Anesthesiology, Pharmacology & Therapeutics, University of British Columbia, Vancouver, BC, Canada
d Centre for Heart Lung Innovation, University of British Columbia, Vancouver, BC, Canada

ABSTRACT
Sepsis remains a leading cause of maternal morbidity and mortality. Recognition and treatment of maternal sepsis are often delayed due to the physiological adaptations of pregnancy and vague or absent signs and symptoms during its initial presentation. Over the past decade, our understanding of sepsis has evolved and maternal early warning systems have been developed in an effort to help providers promptly identify and stratify parturients who are at risk. In addition, new consensus definitions and care bundles have recently been published by the World Health Organization and the Surviving Sepsis Campaign to facilitate earlier recognition and timely management of sepsis. In this narrative review, we summarize the available evidence about sepsis and provide an overview of the research efforts focused on maternal sepsis to date. Controversies and challenges surrounding the anesthetic management of parturients with sepsis or at risk of developing sepsis during pregnancy or the puerperium will be highlighted.

Keywords: Pregnancy; Sepsis; Puerperium; Obstetric anesthesia; Maternal sepsis

Introduction
Sepsis during pregnancy and the puerperium remains a leading cause of maternal morbidity and mortality worldwide. The frequent publications from the World Health Organization (WHO), the Surviving Sepsis Campaign (SSC) and the Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries collaboration (MBRRACE-UK) are highlighting the importance and persistence of this problem. The failure to recognize sepsis and institute prompt treatment underlies most cases of maternal sepsis with poor outcomes. The physiological adaptations in pregnancy, combined with the high rates of trauma and surgical intervention that occur during the peripartum periods, put pregnant women at risk of developing infections that may go unrecognized until there is substantial clinical deterioration. The initial alteration of hemodynamics may be falsely attributed to labor pain or blood loss subsequent to delivery. Moreover, normal laboratory values in obstetric patients differ from non-obstetric patients, and much of what is established and used to define sepsis in the general population has not been fully validated in pregnancy. Efforts to implement early warning systems, revise the definition of sepsis, and develop maternal sepsis care bundles, stem from the knowledge that early recognition, diagnosis and management of maternal sepsis lead to better maternal and fetal outcomes. In this narrative review, we summarize the recent changes in sepsis definitions, provide an overview of maternal sepsis and review the current evidence on early warning systems. Furthermore, we discuss strategies, controversies and challenges surrounding the anesthetic management of parturients with sepsis, or at risk of developing sepsis, during pregnancy and the puerperium.

Scope of the problem
Globally, sepsis is the direct cause of over 260,000 maternal deaths a year; approximately 5% of maternal deaths in developed countries and 11% of maternal deaths in developing nations. Approximately 1 in 1000 women giving birth will develop severe infection with a systemic inflammatory response; half of these will progress to sepsis with organ dysfunction and 3–4% to septic shock. While the absolute risk of death from maternal sepsis is low in developed countries such as the United
States (US) (0.1 per 100000) and United Kingdom (UK) (0.6 per 100000, based on the most recent report by MBRRACE-UK covering 2013–2015; and having fallen from 2.0 per 100000 in 2009–2012), the risk of morbidity from maternal sepsis remains high. For every parturient who dies from sepsis, 50 women are estimated to suffer severe maternal morbidity (SMM) from sepsis, which includes any unexpected outcomes of labor and delivery that result in significant short- or long-term consequences to a women’s health, as defined by the Centers for Disease Control and Prevention. Severe maternal morbidity may lead to fetal morbidity, including fetal infection, preterm delivery and fetal demise. Long-term complications such as chronic pelvic pain, pelvic adhesions and secondary infertility can also result.

### Definitions

#### Evolution of sepsis definitions

The original definitions of sepsis and its related disorders are now over 20 years-old and have undergone significant changes. The following table summarizes the previous and revised definitions of sepsis.

**Table 1** Previous and revised definitions of sepsis

<table>
<thead>
<tr>
<th>PREVIOUS DEFINITIONS</th>
<th>REVISED DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PREVIOUS DEFINITIONS</strong></td>
<td><strong>REVISED DEFINITION</strong></td>
</tr>
<tr>
<td><em>Systemic inflammatory response syndrome (SIRS):</em> a systemic inflammatory response manifested by two or more of the following conditions: (1) temperature &gt;38 °C or &lt;36 °C; (2) heart rate &gt;90/min; (3) respiratory rate &gt;20/min or PaCO(_2) &lt;32 mmHg; and (4) white blood cell count &gt;12 000 or &lt;4000/mm(^3), or &gt;10% immature neutrophils</td>
<td><strong>Sepsis:</strong> a life-threatening organ dysfunction caused by a dysregulated host response to infection. Severity of organ dysfunction is assessed using the Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score.(^{20}) Organ dysfunction can be identified as an acute change in total SOFA score ≥2 points, consequent to the infection. Baseline SOFA score should be assumed to be zero unless patient is known to have pre-existing organ dysfunction</td>
</tr>
<tr>
<td><em>Sepsis:</em> SIRS associated with infection</td>
<td><strong>Septic shock:</strong> Sepsis with persistent hypotension requiring vasopressors to maintain mean arterial pressure (MAP) ≥65 mmHg and a serum lactate level &gt;2 mmol/L (18 mg/dL)</td>
</tr>
<tr>
<td><em>Severe sepsis:</em> Sepsis complicated by organ dysfunction, hypoperfusion, or hypotension</td>
<td></td>
</tr>
<tr>
<td><em>Septic shock:</em> Severe sepsis with persistent hypotension despite adequate volume resuscitation or need for inotropic or vasopressor agents</td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 1** Evolution of sepsis definitions. SIRS: systemic inflammatory response syndrome. SOFA: Sequential (Sepsis-related) Organ Failure Assessment. qSOFA: quick SOFA.
several revisions by multinational societies (Table 1, Fig. 1). In 2001, the original definitions were retained, despite an admission that they lack specificity, and hopes were raised for future biomarkers to aid future diagnosis.12 Recently, definitions and clinical criteria were updated in the 2016 Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).13 The new definitions acknowledge that sepsis is not simply an infection with two or more systemic inflammatory response syndrome (SIRS) criteria, and that there are three essential components to sepsis: infection, host response to infection and organ dysfunction.14 Since the inclusion of organ dysfunction in the definition of sepsis in Sepsis-3, the concept of ‘severe sepsis’ no longer exists. Thus, the Sepsis-3 ‘sepsis’ definition is equivalent to ‘severe sepsis’ used in previous publications, irrespective of SIRS status. Epidemiological figures and study outcomes quoted are from publications prior to the adoption of this new terminology, although in this review we use Sepsis-3 terminology for consistency.

The new WHO maternal sepsis consensus definition is developed from Sepsis-3 and is based on a systematic review of literature and expert consultations.15

Assessment of organ dysfunction
Organ dysfunction or failure may manifest in different ways. In 4158 cases of maternal sepsis in the US, respiratory dysfunction was seen to be most common at 34%, followed by coagulopathy (19%), kidney injury (16%), cardiovascular dysfunction (12%), hepatic dysfunction (10%) and altered consciousness (8%).7 Sepsis in obstetric patients can become rapidly fatal, with a large study from the Netherlands demonstrating that time from first symptom of infection to ‘full blown sepsis’ was less than 24 hours in 39% of patients, and time from infection to death was less than 24 hours in 50% of patients.16 In the UK, a national study of maternal sepsis showed that in 75% of women with a Group A Streptococcal infection, there was less than nine hours between the first signs of systemic infection to the diagnosis of sepsis with organ dysfunction; and in 50% of women, this was less than two hours.17

The presence of organ dysfunction can effectively be identified by a predictive scoring system called the Sequential (or Sepsis-related) Organ Failure Assessment (SOFA) score (Table 2). Organ failure-based scores appear to be superior to obstetric-specific scoring systems and APACHE II scores.18,19 The SOFA score was originally developed to sequentially assess the severity of organ dysfunction from sepsis.20 When measured serially, it can facilitate the identification of septic patients in the Intensive Care Unit (ICU) who are at a higher risk of death, with statistically greater predictive validity than SIRS criteria.21 For patients outside the ICU, a bedside assessment tool called the quickSOFA (qSOFA) score predicts in-hospital mortality with statistically greater predictive validity than SOFA and SIRS.22,23 The qSOFA scoring system is quicker and simpler to use, without the need to wait for laboratory results. This is an advantage given the increasing emphasis on the early recognition of sepsis (Table 3). The qSOFA score ranges from 0 to 3 points; the presence of 2 of 3 qSOFA points in adult patients with suspected infection indicates a greater risk of death or prolonged ICU stay.22

The SOFA and qSOFA criteria may be used without modification in the obstetric population. Among obstetric patients admitted to the ICU, the mean total SOFA

### Table 2: Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score

<table>
<thead>
<tr>
<th></th>
<th>SOFA 1</th>
<th>SOFA 2</th>
<th>SOFA 3</th>
<th>SOFA 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiration: PaO2/FiO2, mmHg (kPa)</td>
<td>&lt;400 (53.3)</td>
<td>&lt;300 (40)</td>
<td>&lt;200 (26.7) with respiratory support</td>
<td>&lt;100 (13.3) with respiratory support</td>
</tr>
<tr>
<td>Coagulation:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets x 10^3/µL</td>
<td>&lt;150</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Liver: bilirubin, mg/dL (µmol/L)</td>
<td>1.2–1.9 (20–32)</td>
<td>2.0–5.9 (33–101)</td>
<td>6.0–11.9 (102–204)</td>
<td>&gt;12.0 (204)</td>
</tr>
<tr>
<td>Cardiovascular:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>MAP &lt;70 mmHg</td>
<td>dopamine ≤5 µg/kg/min, or dobutamine (any dose)</td>
<td>dopamine &gt;5 µg/kg/min, or epinephrine ≤0.1 µg/kg/min, or norepinephrine ≤0.1 µg/kg/min</td>
<td>dopamine &gt;15 µg/kg/min, or epinephrine &gt;0.1 µg/kg/min, or norepinephrine &gt;0.1 µg/kg/min</td>
</tr>
<tr>
<td>Central nervous system:</td>
<td>13–14</td>
<td>10–12</td>
<td>6–9</td>
<td>&lt;6</td>
</tr>
<tr>
<td>Glasgow Coma Scale Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal: serum creatinine, mg/dL (µmol/L) or urine output</td>
<td>1.2–1.9 (110–170)</td>
<td>2.0–3.4 (171–299)</td>
<td>3.5–4.9 (300–440), or urine output ≤500 mL/day</td>
<td>&gt;5.0 (440) or urine output &lt;200 mL/day</td>
</tr>
</tbody>
</table>

PaO2: partial pressure of oxygen; FiO2: fraction of inspired oxygen; MAP: mean arterial pressure.

*Adapted from Vincent et al.20*
The physiological changes of pregnancy overlap with hemodynamic changes associated with the initial presentation of sepsis. For example, tachycardia represents a normal physiological adaptation to pregnancy and may also result from pain and increased maternal effort required during second stage labor. The expanded plasma volume in pregnancy and progesterone-induced vasodilatation allow women to compensate for longer before rapid deterioration.29 Furthermore, elevation in white blood cell count is a normal finding during pregnancy, making this parameter less distinctive in the forewarning of an activated host immune response. Moreover, signs of systemic inflammation may be present in various stages of labor and delivery, as a result of prostaglandin treatment for induction of labor or treatment of postpartum hemorrhage. A high index of suspicion, with a detailed history and examination, are therefore paramount for the early recognition of maternal sepsis. The 2014 report by MBRRACE-UK states ‘think sepsis’ when presented with any unwell pregnant, or recently pregnant, patient.30

Maternal signs and symptoms will vary depending on the source of sepsis, but particularly ominous signs are tachypnea, neutropenia, hypothermia and altered mental status.2 Presentation may be associated with early pregnancy loss, intrauterine death, fetal tachycardia or fetal bradycardia. While fever is often the first vital sign change that raises the index of suspicion of maternal sepsis for clinicians, temperature alone is not a reliable indicator of sepsis. In the Michigan series of maternal deaths, 73% of women who died of sepsis were afebrile at presentation and 25% did not develop a fever at all during their hospitalization.31

### Maternal early warning scoring systems

In the last decade, multiple early warning scoring systems have been developed to facilitate timely identification of septic patients at risk for poor outcomes. Unfortunately, many of these systems, such as the Modified Early Warning System (MEWS), have not proven to be as useful as hoped in the maternal population, because they do not take into account the physiological changes of pregnancy, which overlap with clinical criteria for diagnosing sepsis in the general population.32 Attempts have been made to adapt existing scores for the obstetric population – for example, the ‘Sepsis in Obstetrics Score’ has a higher positive predictive value for admission to the ICU (16.7%) than its non-obstetric comparators – the Rapid Emergency Medicine Score (11.1%) and the MEWS (4.6%).33 In the US, the National Council for Patient Safety proposed the use of the maternal early warning criteria (MERC)34 and in the UK, the 2007 Confidential Enquiry into Maternal and Deaths report recommended routine use of the Modified Early Obstetric Warning System (MEOWS).2 While uptake of maternal early warning systems following the recommendation has been high over the past 10 years,35 clear evidence of outcome benefit is lacking36 and validation studies have shown high sensitivity but low specificity.37–39 Neither

### Diagnosis and recognition of maternal sepsis

#### Challenges in early recognition of maternal sepsis

The physiological changes of pregnancy overlap with hemodynamic changes associated with the initial presentation of sepsis. For example, tachycardia represents a normal physiological adaptation to pregnancy and

### Risk factors for maternal sepsis

Several risk factors for maternal sepsis have been identified,2,6,25 leading to the widespread implementation of guidelines for the prevention of sepsis in this vulnerable patient population. It is now routine to screen and treat asymptomatic bacteriuria (present in 2–7% of pregnant women)26 and sexually transmitted diseases27 in early pregnancy and to administer antibiotic prophylaxis for cesarean delivery.28 Importantly, women who are treated with antibiotics in the perinatal period have been found to remain at risk of sepsis and septic shock, suggesting that a proportion of infections progress following antibiotic treatment.17 Sepsis is more common in parturients who are more than 35 years-old; and those that have co-morbid conditions such as diabetes mellitus and obesity, as well as those who have had invasive or surgical procedures. With the increase in maternal age, success of assisted reproductive technologies and increased rates of cesarean delivery, a large proportion of parturients will have at least one risk factor for maternal sepsis.

#### Diagnosis and recognition of maternal sepsis

### Table 3 Quick sepsis-related organ failure assessment score (qSOFA) 

<table>
<thead>
<tr>
<th>Assessment</th>
<th>qSOFA score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachypnea: (&gt;22 breaths/min)</td>
<td>1</td>
</tr>
<tr>
<td>Hypotension: (SBP &lt; 100 mmHg)</td>
<td>1</td>
</tr>
<tr>
<td>Altered mentation: (GCS &lt;15)</td>
<td>1</td>
</tr>
</tbody>
</table>

SBP: systolic blood pressure; GCS: Glasgow Coma Scale.

*aAdapted from Singer et al.22*
the MERC nor the MEOWS have been formally evaluated to determine if their use might lead to a reduction in maternal morbidity.

A recent large, prospective, multicenter impact study by Shields et al.\(^1\) investigated whether maternal morbidity could be reduced with the implementation of the ‘Maternal Early Warning Trigger (MEWT)’ tool. Unlike the MERC and MEOWS, the MEWT tool was designed to identify four of the major causes of maternal morbidity resulting in ICU admission (i.e. sepsis, cardiopulmonary dysfunction, preeclampsia-hypertension and hemorrhage), and includes prompts to help expedite patient assessment, investigation, management and a differential diagnosis (for example it reminds providers to consider the overlap in signs and symptoms between sepsis and cardiopulmonary dysfunction). Using the CDC-defined SMM and composite maternal morbidity (at least one of CDC-defined SMM, namely hemorrhage >500 mL for vaginal delivery or 1000 mL for cesarean delivery without transfusion; need for dilation and curettage; or ICU admission) as outcome measures, the authors found that using the MEWT tool led to a significant reduction in CDC-defined SMM (−18.4%, \(P=0.01\)) and in composite maternal morbidity (−13.6%, \(P=0.01\)) when compared to pre-implementation of the MEWT tool. Despite these promising results, the positive predictive value for predicting sepsis was only 7% and the authors acknowledged that the MEWT tool may not be generalizable to centers with a low rate of sepsis. This finding is consistent with others that have noted the poor ability of screening tools to predict maternal sepsis.\(^32,36\)

Maternal early warning scores need further refinement to improve their ability to predict those with signs of early sepsis and at risk of deterioration. The development of obstetric scoring systems is, in part, hindered by the lack of consensus regarding which vital signs should be used and what values reflect normality in the obstetric population.\(^31\) It has even been suggested that these values should change depending on the stage of pregnancy in which they are being measured.\(^42\) The Pregnancy Physiology Pattern Prediction Study (4P Study) aims to develop a database of physiology during pregnancy and the postpartum period (NCT01509378). It will provide data to define pregnancy-specific thresholds at which an alert should be triggered and from which more robust evidence-based scores can be developed.\(^43\)

### Management of maternal sepsis

#### Sepsis care bundles

**Sepsis care bundles**

Shortly after the 2001 consensus conference, the SSC was launched by the Society for Critical Care Medicine (SCCM), the European Society for Intensive Care Medicine (ESICM), and the International Sepsis Forum (ISF), with a goal of reducing sepsis mortality by 25% in five years. They published management guidelines, together with condensed versions of these guidelines or ‘care bundles’. Care bundles are groups of interventions designed to guide the timing and implementation of individual elements of care to improve outcome. The first care bundles for sepsis were published in 2003,\(^44\) drawing many recommendations from those described by Rivers et al. in the landmark randomized controlled trial (RCT) of Early-Goal Directed Therapy (EGDT) in 2001.\(^45\) They have since been updated in 2008,\(^46\) 2012,\(^47\) and most recently in 2016\(^48\) (Table 4), to take into account the publication of three large RCTs on EGDT, all of which demonstrated no mortality benefit after initial volume resuscitation was complete and early antibiotic treatment had been initiated.\(^49-51\) Survival in all three of these trials was much better than the original Rivers study,\(^45\) suggesting that the management of septic shock has improved with early implementation of protocol-driven care, even if not strictly adherent to the original EGDT protocol. The Royal College of Obstetricians and Gynaecologists (RCOG) recommends that sepsis should be managed in accordance with the care bundles,\(^52\) because there is evidence to suggest that

<table>
<thead>
<tr>
<th>To be completed within 3 hours of time of presentation:</th>
<th>Strength of recommendation, grade of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Measure lactate level</td>
<td>Weak, low quality</td>
</tr>
<tr>
<td>2. Obtain blood cultures prior to administration of antibiotics</td>
<td>Best practice statement</td>
</tr>
<tr>
<td>3. Administer broad spectrum antibiotics</td>
<td>Strong, moderate quality</td>
</tr>
<tr>
<td>4. Administer 30 mL/kg crystalloid over the first three hours for hypotension or lactate ≥4 mmol/L</td>
<td>Strong, low quality</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>To be completed within 6 hours of time of presentation:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure ≥65 mmHg</td>
<td>Strong, moderate quality</td>
</tr>
<tr>
<td>6. In the event of persistent hypotension after initial administration (MAP &lt;65 mmHg) or if initial lactate was ≥4 mmol/L, reassess volume status and tissue perfusion and document findings</td>
<td>Best practice statement</td>
</tr>
<tr>
<td>7. Re-measure lactate if initial lactate elevated</td>
<td>Weak, low quality</td>
</tr>
</tbody>
</table>

\(^a\)Adapted from survivingsepsis.org\(^26\) MAP: mean arterial pressure.
survival in sepsis is improved by following this guidance.53 The elements of the bundles are based on the currently available evidence and are designed to be completed in a specific time period. For each element, the strength of recommendation and grade of evidence are provided, or it is described as a ‘best practice statement’. No modifications are suggested for the care of obstetric patients. The UK Sepsis Trust has recently developed a specific ‘sepsis toolkit’ for use in pregnancy and up to six weeks postpartum.

This decision support tool is based on the 2016 National Institute for Health and Care Excellence (NICE) recommendations on maternal sepsis, published after the preceding MBRRACE-UK report.55

It must be remembered that almost all the evidence used to develop management guidelines for sepsis are based on RCTs in which pregnancy was an exclusion criterion. To date, there are no large-scale studies of sepsis management in the obstetric population, due to ethical challenges in conducting randomized research in septic parturients. The management of sepsis in the obstetric population is therefore largely extrapolated from that of the general population (see Appendix A).

**Antimicrobial therapy**

Observational studies have repeatedly demonstrated that delay in initiation of antimicrobial therapy is associated with poor outcome in sepsis. In an international, multicenter study of over 17990 patients with sepsis or septic shock, there was a linear increase in mortality per hour of delay in administration of antibiotics upon recognition of sepsis.56 Similar results were demonstrated in two recent retrospective studies involving 35000 septic patients from 21 emergency departments and over 40000 septic patients reported to the New York State Department of Health.57 These data suggest that antibiotics should be commenced as soon as possible after collection of blood cultures and within the first hour of diagnosis.

The genitourinary tract is colonized with a large variety of organisms. Not all of these cause infection and sepsis but pregnant women who develop sepsis are likely to be infected by more than one organism.59 Therefore, the initial choice of antibiotic should be broad and based on local guidelines and patterns of resistance, especially if the source is unknown. Because Group A Streptococcus (GAS) and Escherichia coli are the most common contributors to sepsis in pregnancy and responsible for a significant proportion of deaths, empiric coverage should include these organisms. Compared to vaginal delivery, cesarean delivery confers a five to 20-fold increase in risk of infection and morbidity:28,60 this risk can be substantially reduced by the use of prophylactic antibiotics preoperatively.61 Although GAS is sensitive to \( \beta \)-lactam antibiotics in vitro, sensitivity does not always predict efficacy. Protein synthesis inhibitors (e.g., clindamycin) have been demonstrated to be more effective than \( \beta \)-lactams in animal models of GAS infection62 and therefore, the Infectious Diseases Society of America (IDSA) recommends that patients with invasive GAS infection promptly receive penicillin (2–4 million units every 4–6 hours intravenously) plus clindamycin (600–900 mg every 8 hours intravenously) for 10–14 days.63

Early involvement of an infectious disease specialist can help with optimization of antimicrobial therapy, especially when there is failure to respond to first-line treatment.64 Once the culture and sensitivity information is available, the spectrum of coverage should be narrowed. Individualized antibiotic dosing may help improve mortality in the sickest septic patients.65 In accordance with the new SSC guidelines, dosing strategies should be based on pharmacokinetic and pharmacodynamic principles where possible. This recommendation is based on the observation that initial doses of antibiotics are often insufficient due to an increase in volume of distribution and augmented renal clearance,66 two physiological changes invoked by pregnancy. Moreover, maternal obesity is increasing worldwide67 and is an independent risk factor for maternal sepsis.68 Standard dosing of antibiotics in the obese parturient may be inadequate due to altered pharmacokinetics and tissue penetration. Swank et al.69 found that using 3 g instead of 2 g of prophylactic cefazolin at the time of cesarean delivery, significantly more women with body mass index >30 kg/m² were able to achieve the recommended minimum inhibitory concentration for cefazolin. Other proposals to reduce infections in the obese population include topical and subcutaneous antibiotic regimens,70,71 prophylactic subcutaneous drains72 and complex wound dressings.73–75

**Fluid therapy**

Fluid management is challenging in a septic parturient. A persistent positive fluid balance has been shown to be an independent risk factor for mortality in sepsis.76 Despite its low incidence, fluid overload and pulmonary edema have contributed to maternal morbidity and mortality.2 Concomitant use of oxytocin, pre-existing cardiac disease or preeclampsia may further complicate fluid management. The improvement in survival from preeclampsia is largely attributable to more cautious restrictive fluid regimens.77 The SSC guidelines recommend crystalloid at an initial 30 mL/kg bolus; however, this may be too aggressive in the obstetric population. The choice of crystalloid has long been debated but there is evidence that balanced crystalloid solutions are associated with a lower mortality in sepsis as compared to normal saline.78
Measuring adequacy of resuscitation

The goal in sepsis resuscitation is to restore normal tissue perfusion. Central venous oxygen saturation (ScvO2) and central venous pressure (CVP) have been used as markers for adequate tissue perfusion and volume replacement.\(^{35}\) However, these measurements require the insertion of a central venous catheter and current evidence does not support its widespread adoption. The optimal CVP is unknown in pregnancy and is a poor marker of intravascular volume.\(^{79,80}\) Furthermore, ScvO2 has not been consistently shown to be a good prognostic indicator or predictor of fluid responsiveness;\(^{81}\) however, very high ScvO2 levels are associated with increased mortality in sepsis and may reflect impairment of the microcirculation and mitochondrial dysfunction.\(^{82,83}\) Using serum lactate clearance to guide resuscitation in septic shock was shown to result in similar mortality as using ScvO2.\(^{84}\) However, neither lactate clearance nor central venous-to-arterial carbon dioxide pressure difference (ΔP\(_{\text{V-A}}\)CO\(_2\)) have been shown to consistently indicate an end-point to treatment or to guide further treatment to improve outcome.\(^{85}\) Recent consensus recommendations in cardiac output monitoring suggest that echocardiography should be the preferred method for diagnosis and sequential monitoring of response to resuscitation in shock, and that invasive cardiac output monitoring is only required in those that do not respond to initial treatment.\(^{86}\) Overall, there is a trend away from more invasive to less invasive methods of cardiac output monitoring. The new SSC guidelines accordingly state volume status and tissue perfusion may be assessed with either focused clinical examination or two of the following: CVP, ScvO2, bedside cardiac ultrasound, or dynamic assessment of fluid responsiveness via passive leg raise (PLR) or fluid challenge.\(^{87}\)

For many obstetric units, the equipment and knowledge to perform bedside echocardiography may not always be obtainable. It has been suggested that PLR is a quick, non-invasive and reversible way to assess for fluid responsiveness,\(^{88}\) with some evidence to suggest the hemodynamic response is similar between non-pregnant controls and pregnant women at 22–24 weeks’ gestation.\(^{89}\) A standard PLR challenge does require direct measurements of cardiac output and stroke volume using a non-invasive cardiac monitor, or other reliable surrogates such as changes in carotid or femoral Doppler response before and after the maneuver.\(^{90}\) To perform this on a pregnant patient, after obtaining baseline measurements in a 45° semi-recumbent position with left lateral displacement of ≥30° to minimize aortocaval compression, the head of the bed is flattened and the legs are elevated to 45° for 30 seconds while maintaining uterine displacement. One small study in spontaneously breathing healthy volunteers found that PLR was 72% sensitive (95% CI 55% to 85%) and 100% specific (95% CI 40% to 100%) for predicting the presence of fluid responsiveness.\(^{91}\) In ventilated patients, an increase in the cardiac output or a surrogate measure, such as mean arterial pressure (MAP) of ≥10%, after PLR indicates fluid-responsiveness.\(^{92}\) While this remains to be validated in the maternal sepsis population, PLR may represent a useful alternative in units without access to echocardiography.

Vaspressors and inotropes

Sepsis-mediated hypotension is the result of venous and arterial vasoplasia, relative hypovolemia and myocardial depression. If vasopressors are required to maintain MAP after fluid resuscitation, SSC recommends norepinephrine as the first-line agent,\(^{93}\) although a target MAP may need to be individualized, as a MAP of 65 mmHg may well be too high in a previously healthy, young patient. The MAP should therefore be interpreted with reference to organ perfusion, urine output, lactate clearance and fetal heart rate tracing if applicable, which will give information about placental perfusion.\(^{47,94}\) Again, the SSC guidelines are based on evidence from non-pregnant patients and there are little data on the effect on placental blood flow of vasopressors, although in a dual-perfused single-cotyledon human placental model, norepinephrine did not affect perfusion on the ‘fetal side’.\(^{95}\)

Regional anesthe sia

Neuraxial techniques are generally deemed to be relatively contraindicated in the septic patient. First, the presence and degree of systemic vasodilation and cardiovascular compromise in sepsis makes further sympathetic blockade resulting from neuraxial techniques dangerous. Second, there may be concomitant thrombocytopenia or coagulopathy, increasing the risk of bleeding complications. Third, there may be an increased risk of meningitis and epidural or spinal abscess. A recently updated joint report from the American Society of Anesthesiologists (ASA) and the American Society of Regional Anesthesia (ASRA) recommends individualized plans in patients with suspected sepsis where neuraxial techniques are considered.\(^{96}\) Specifically, the guidelines recommend that providers should consider pre-procedure history, physical examination, and review laboratory results, when considering alternatives in patients that are ‘high risk’—although the term ‘high risk’ is not defined. In addition, the use of prophylactic antibiotics for suspected bacteremic patients is advocated and selection of the neuraxial technique should be made on a case-by-case basis.\(^{96}\) These recommendations are based on case reports, case series and surveys of practice and are not specific to the obstetric population.

The obstetric anesthesiologist is frequently faced with a dilemma when a febrile parturient with suspected chorioamnionitis is requesting epidural labor analgesia.
There is concern that a neuraxial technique may result in seeding of the epidural or subarachnoid space in a bacteremic patient. It is difficult to base a decision on whether to perform neuraxial anesthesia on laboratory results, due to the normal increase in white cell count in labor, and the poor correlation between white cell count and presence of bacteremia in pregnancy.97 Few guidelines exist to guide the use of neuraxial techniques in the septic or bacteremic parturient.

Fortunately, infections related to labor epidural analgesia are extremely rare in obstetric patients. This is likely due to relatively short catheter durations (recent evidence in the non-obstetric population indicates that infection risk with epidural catheterization increases over time, especially after four days),98 the use of prophylactic antibiotics in chorioamnionitis and operative delivery, and the fact that this population is generally healthy. The Third National Audit Project (NAP 3) of The Royal College of Anaesthetists found an incidence of 1 in 47,000 cases of epidural abscess in the whole population of the project, with only one case in an obstetric patient.99 Another retrospective review found only one case in 50,500 women who received epidural anesthesia for vaginal or cesarean delivery over a four-year period.100 Although epidural abscesses are rare in the obstetric population and often attributed to a break in sterile technique, the presence of underlying medical conditions such as diabetes may increase the baseline risk. To complicate matters, epidural abscesses have also occurred in low-risk postpartum women who did not receive neuraxial analgesia.101

The risk of central infection from neuraxial techniques is deemed to be very small in patients treated with antibiotics.99,102 The current recommendation suggests that patients with evidence of systemic infection may safely receive single-shot spinal anesthesia, provided antibiotics have been commenced and a response to treatment has been demonstrated.102 However, the placement of an indwelling epidural catheter is more controversial, although similar criteria are often used in a clinical setting.

At present, there is no consensus on neuraxial techniques in obstetric patients with intrapartum fever, bacteremia or sepsis. In a UK national survey sent to all members of the Obstetric Anaesthetists Association (OAA) via their approved survey system, there was significant variation in provider responses in relation to insertion of labor epidural catheters in the presence of intrapartum fever. In this survey of 571 anesthesiologists, which was limited by only a 31% response rate, 31% stated they would site an epidural after antibiotics, 30% would site an epidural without antibiotics, 22% would decide on a case-by-case basis, and 17% would refuse to site an epidural and offer alternative analgesia.103 The findings of this survey highlight a need for clearer guidance on this matter; however, the lack of robust, high-quality evidence currently defies a definitive statement on the risk of central nervous system infection in patients with chorioamnionitis or bacteremia undergoing regional anesthesia.

**General anesthesia**

General anesthesia is often required in a septic parturient due to the inability to safely provide regional anesthesia or the need to control ventilation and hemodynamics. The same precautions should be taken for all pregnant and postpartum patients undergoing general anesthesia, taking into account their increased risk of aspiration, aortocaval compression from the gravid uterus in the supine position, laryngeal edema exacerbated by fluid resuscitation leading to increased risk of difficult intubation, and the degree of cardiovascular compromise due to sepsis.104 In the severely compromised patient, ketamine may be considered instead of propofol as the induction agent for general anesthesia.105 Once general anesthesia is achieved, invasive monitoring should be placed to assist detection of early hemodynamic changes and to guide vasopressor and inotropic support. Early consultation of an intensivist and transfer of the patient to ICU should be considered. Effective communication with critical care physicians is vital. Often serious incident and root-cause analysis will be required to learn from what is a relatively rare event in the majority of hospitals.106,107

**Delivery considerations**

The decision of whether as to deliver the fetus or continue the pregnancy is influenced by a number of factors including the patient’s condition, the gestational age of the fetus, the fetal condition, the presence of chorioamnionitis and the stage of labor. Attempting early delivery in patients with severe cardiovascular compromise due to sepsis may increase maternal and fetal mortality,108 unless chorioamnionitis is suspected as the source of sepsis or a septic abortion has occurred.59,109 If the risks of continuing the pregnancy outweigh those of early delivery, administration of antenatal steroids and magnesium should be considered to improve the outcome of a premature fetus.110 Decisions relating to delivery of the baby are ultimately the responsibility of the obstetrician, although the anesthesiologist may advise on timing in relation to resuscitation of the mother. Collaboration and discussion with the neonatal, intensive care and microbiology teams; and the patient, are also vital. If surgical intervention for source control, including cesarean section, is required, the decision about whether to proceed under regional or general anesthesia should be made on a case-by-case basis, having considered the risks and benefits of each approach. To date, no large, RCTs has addressed the question of whether neuraxial or general anesthesia would result in better or worse outcomes in maternal sepsis.
One of the goals of sepsis management in the perinatal period is to maintain oxygenation and perfusion of vital organs and the placenta, whilst identifying the source of infection and treating it. In the antenatal period, maternal resuscitation is the key to ensuring fetal wellbeing.111,112 Antepartum sepsis arising from the uterus will require delivery for source control, despite the fact that neonatal survival is correlated with gestational age. Attempts to delay delivery in this setting are often too dangerous for the mother. Sepsis arising antenatally from a non-uterine source is a more difficult scenario. When sepsis is diagnosed in the antepartum period, one prospective case-control study of a national database in the UK from 2011 to 2012 found the median (IQR) gestational age to be 35 weeks (27–40 weeks) and the diagnosis-to-delivery interval to be zero days (1–7 days).9

Future developments

The overlapping physiological changes of pregnancy and clinical features of sepsis in this high-risk patient population would make a reliable biomarker particularly useful. There is currently no ideal biomarker that can indicate prognosis, predict progression of the disease and guide treatment in sepsis. Early identification of those at risk of developing life-threatening septic shock would enable early triage and treatment. Biomarkers could also aid the differentiation of sepsis from non-infective systemic inflammation in the intensive care community, and in the parturient, and may help distinguish likely benign ‘epidural fever’ from infectious. This could reduce the unnecessary use of antibiotics in both mothers and neonates, in an age of increasing antimicrobial resistance.

Procalcitonin (PCT), a pro-inflammatory biomarker, has been studied to help differentiate bacterial sepsis from non-infective SIRS and guide antimicrobial stewardship decisions.113 However, a PCT-guided antimicrobial escalation strategy did not improve survival, and in fact prolonged ICU admission.114 A recent large, prospective US study showed that PCT levels that do not decrease by more than 80% independently predict mortality in sepsis;115 however, it remains unclear what measures should be used in patients with non-decreasing PCT levels to improve outcomes.

Other potential areas of interest in developing novel biomarkers are endothelial proteins, such as angiopoietins; cell surface receptors, such as leucocyte surface receptors; cytokine/chemokine signaling molecules; immunomodulatory biomarkers; and potential genomic regulators.116 The ExPRES-Sepsis Study that is currently in progress aims to explore the predictive value of leucocyte surface markers in sepsis.117 Ultimately, with a better understanding of the pathophysiology and cellular processes driving sepsis, we can better define sepsis as a set of distinct biochemical disorders that can be targeted when creating diagnostic tests and therapies.

Many challenges remain in the diagnosis and management of maternal sepsis. Further research is needed to establish robust diagnostic criteria for sepsis and septic shock in the obstetric population and then develop specific protocols accordingly. The new maternal definition and identification criteria will be tested and validated in a large global one-week cross-sectional study—the Global Maternal Sepsis Study.118 Information on prevention and management will be collected to inform the development of strategies for reducing maternal infections and sepsis in all-income countries. The Global Maternal and Neonatal Sepsis Initiative will further the development of identification criteria, prevention strategies and management bundles, with the aim of accelerating the reduction of preventable sepsis deaths during pregnancy and the puerperium by 2030.118

References


49. Royal College of Obstetricians and Gynaecologists. Sepsis following Pregnancy, Bacterial (Green-top Guideline No 64b). 2012.
C.E.G. Burlinson et al.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijoan.2018.04.010.