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SOMANZ guidelines for the investigation and management sepsis in pregnancy

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Abstract:

SOMANZ (Society of Obstetric Medicine Australia and New Zealand) has written a guideline to provide evidence based guidance for the investigation and care of women with sepsis in pregnancy or the postpartum period. The guideline is evidence based and incorporates recent changes in the definition of sepsis. The etiology, investigation and treatment of bacterial, viral and non-infective causes of sepsis are discussed. Obstetric considerations relevant to anesthetic and intensive care treatment in sepsis are also addressed. A multi-disciplinary group of clinicians with experience in all aspects of the care of pregnant women have contributed to the development of the guidelines. This is an executive summary of the guidelines.

Background

Despite an overall decline in maternal mortality in Australia, the maternal mortality rate from sepsis has increased from 0.6 per 100,000 in 2003-2005 to 0.8 per 100,000 in 2008-2012¹. In the period 2008-2012, sepsis accounted for 11.4% of maternal deaths in Australia¹. Group A beta hemolytic streptococcal (GAS) infection is the most common pathogen resulting in 25% of maternal deaths from sepsis in both Australia and the UK². The ninth Perinatal and Maternal Mortality Review Committee: report on maternal deaths in NZ³ between 2006-2013 indicates 50% of deaths from sepsis were related to Group A streptococcus. Sepsis continues to be one of the major causes of maternal mortality among Aboriginal and Torres Strait Islander women¹.

In Australia, the Clinical Excellence Commission developed the “Sepsis Kills” program to reduce poor outcomes from sepsis by improving recognition and management⁴. A specific maternal pathway was created⁵. Sepsis can arise at any time during pregnancy and is often associated with a delay in diagnosis. The normal physiological changes of pregnancy may mask early signs of sepsis^{6,7}. The woman has a unique ‘organ perfusion monitor’, namely the

fetus. Maternal sepsis with or without hemodynamic instability may present with fetal distress as the uteroplacental circulation is not auto-regulated⁸. Thus any maternal circulatory insufficiency arising from sepsis may result in compromised fetal perfusion. Management plans need to take into consideration the altered immunological response of the woman and altered physiological responses during pregnancy⁹. Consideration needs to be also given to the impact of the condition as well as the effect of its treatment on the fetus. The additional complexity of sepsis therapy in breast-feeding women also requires appropriate consideration.

These are the recommendations of a multidisciplinary working party convened by the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ).

Methods

The clinical evidence for this guideline has been analysed by the authors according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system¹⁰.¹¹. The principles followed in the development of these guidelines include: 1) a systematic review of the evidence with at least the following searches deployed: Cochrane library, Medline and EMBASE. 2) The authors formed a multi-disciplinary team 3) Financial support for administration was provided by SOMANZ. None of the authors received any direct financial compensation for their time to the development of this guideline. Where there were conflicting views, three authors (HR, LB and AM) reviewed the topic and came to a consensus. All authors reviewed the final guideline.

Definition of sepsis in pregnancy

Despite significant advances, understanding of the pathobiology of sepsis remains incomplete and currently no gold standard diagnostic test exists to confirm the presence of sepsis. Sepsis is broadly defined as life-threatening organ dysfunction caused by a dysregulated host response to infection¹². It is this dysregulated response and subsequent organ dysfunction that

differentiates sepsis from infection. The clinical signs may be insidious until sepsis is far advanced, which may occur very rapidly. Therefore early detection of sepsis is essential for appropriate multidisciplinary management to ensure the best outcomes for the mother and her baby. Septic patients may progress to develop septic shock, multi organ failure and death.

Septic shock is defined as a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities substantially increase mortality¹². More recently, the Sequential (sepsis-related) Organ Failure Assessment score (SOFA) has been shown to be useful in identifying those patients with a suspected infection who are likely to have a prolonged ICU (Intensive Care Unit) stay or die in hospital^{12, 13}. A q(quick) SOFA score can be used to identify patients promptly at the bedside using only clinical information¹⁴.

SOMANZ definition of sepsis

Recognising the patient with sepsis is paramount and is the first step in appropriate assessment and management. The flowchart in figure 1 summarises the clinical steps involved in the assessment and management of sepsis in pregnancy.

We recommend using the obstetrically modified qSOFA (omqSOFA) (Table 1). The obstetrically modified SOFA (omSOFA) score should be used for a subsequent, more thorough, assessment.

Obstetrically modified quick SOFA (omqSOFA) score

The qSOFA requires only clinical data for assessment and thus can be performed quickly without waiting for the results of biochemical or laboratory tests¹⁴. In the non-pregnant patient, this score incorporates: systolic blood pressure of 100mmHg or less, respiratory rate of 22/min or greater and altered mentation; Glasgow coma score (GCS) less than 15. For each variable present, a score of 1 is attributed resulting in a score range of 0 - 3. A qSOFA score of greater than or equal to 2 has predictive validity for discriminating patients with an increased risk of in-hospital mortality¹⁴. However, the data from which the score was derived

however, is retrospective and validated in a heterogeneous population, with an average age of 61 years, of whom half were male. Extrapolation to pregnant and postpartum women should be undertaken with caution.

A woman's gravid state will impact some of the variables in the qSOFA. Pregnancy significantly affects systolic blood pressure but not respiratory rate¹⁵ or mentation. During pregnancy, although women normally develop a respiratory alkalosis and compensatory metabolic acidosis, this is not through an increase in respiratory rate¹⁵. The higher respiratory rate of 25 breaths/min, as compared to 22/min derived from published literature, was agreed upon by the writing committee as it aligned with cut offs employed on the maternity observation charts. Respiratory rate is poorly assessed in routine clinical practice¹⁶. Systolic blood pressure usually decreases by 5-10mmHg in pregnancy¹⁷. Furthermore a significant number (approximately 15%) of the obstetric population will have a usual systolic blood pressure at any given gestation, of less than 100mmHg and normal pregnancy outcomes¹⁸.

Given these changes, several modifications are suggested to the qSOFA criteria when applied to pregnancy: obstetrically modified qSOFA (omqSOFA). Using the omqSOFA (Table 1), sepsis (as distinct from infection) in pregnant women should be considered where 2 or more of the following are present:

- Systolic blood pressure of 90mmHg or less
- Respiratory rate of 25/min or greater
- Altered mentation (any state other than 'Alert' on maternal observation charts). GCS (Glasgow coma scores) are not typically formally assessed as part of routine observations in obstetric wards.

Obstetrically modified SOFA (omSOFA) score

If sepsis is suspected based on screening, then assessment for end-organ dysfunction should be undertaken¹². Sepsis has been defined as an acute change in the total SOFA score of ≥ 2 points consequent to infection. The baseline SOFA score is generally assumed to be zero where there is no pre-existing organ dysfunction. In the general population a SOFA of ≥ 2 is associated with an overall mortality of 10%, these data are yet to be validated in the obstetric population. The SOFA score, in observational data, has been found to be significantly higher

in pregnant women who have died compared to those who have survived in an intensive care setting^{19, 20}. However the SOFA score has not undergone appropriate prospective validation in pregnant and postpartum populations. The studies that exist to date have been small, retrospective and undertaken in resource challenged environments which may limit their applicability generally.

This guideline recommends several modifications when applying the SOFA score to pregnancy (obstetrically modified SOFA- omSOFA) as indicated (Table 2):

- In order to demonstrate evidence of end organ dysfunction a score of ≥ 2 needs to be attained. Therefore, scores of 3 or 4 in each category have been removed for the purposes of simplification.
- During pregnancy, serum creatinine levels are significantly reduced with the normal range being 35-80 $\mu\text{mol/L}$ ²¹. For practical purposes, the serum creatinine cut off for the scores of 0, 1 or 2 have been adjusted to <90 $\mu\text{mol/L}$, 90-120 $\mu\text{mol/L}$ or greater than 120 $\mu\text{mol/L}$ respectively²².
- As the GCS is not routinely assessed on maternity wards, the central nervous system category has been changed to reflect the maternal observation charts in routine clinical use. Alert will be scored 0, rousable by voice as 1 and rousable only by pain as 2. Any score other than 0 or 'alert' should trigger a GCS to be performed.
- Healthy pregnant women may have a mean arterial pressure less than 70mmHg. Thus the SOFA score should be interpreted in the context of the woman's premorbid blood pressure.

SOMANZ Definition of septic shock

If sepsis progresses, septic shock may ensue and this is associated with a substantial increase in mortality compared to sepsis alone²³. The clinical criteria validated to identify septic shock in non-pregnant patients include:

- Hypotension requiring vasopressor therapy to maintain a **MAP 65mmHg** or greater (despite adequate fluid resuscitation) and
- Serum lactate **greater than 2mmol/L** after adequate fluid resuscitation²⁴

No alterations have been made to these definitions for pregnancy.

C-reactive protein (CRP) has not been included in the current definition. It lacks sensitivity and is highly variable in pregnancy and should not be used to define or diagnose sepsis²¹. Fever, although helpful in identifying pregnant patients with suspected infections or sepsis, has also not been included, as it lacks sensitivity²⁵ (see section on fever below).

Given that maternal physiology gradually returns to normal postpartum, we recommend the definition of postpartum sepsis be the same as for non-pregnant patients after the first week postpartum.

Key Points 1:

- Screen for sepsis using the omqSOFA score.
- Assess for evidence of end organ dysfunction using omSOFA score
- Septic shock is a complication of sepsis evidenced by the need for vasopressors and elevated lactate

GRADE: MODERATE QUALITY EVIDENCE

the health impacts on the offspring, Dreier and colleagues²⁶ reported an increase in the rate of pregnancies affected by a neural tube defect in mothers who experienced fever in the first trimester or peri-conceptually (pooled odds ratio of 2.9 (95% Confidence Interval [CI] 2.22-3.79)) Oral clefts were also more common in mothers with fever early in pregnancy (OR 1.94, 95% CI 1.35-2.79). Congenital heart defects were weakly associated with early maternal fever early in pregnancy (OR 1.54, 95% CI 1.37-1.74). No effect of maternal fever was seen on the risk of miscarriage, stillbirth or preterm labour.

Human studies appear to vary from animal studies in the absence of a dose-response relationship. In animals where a temperature elevation of greater than 2°C was documented there was a greater risk of teratogenic outcome²⁷. In human studies, reliance on self-reported temperature may lead to inaccurate results²⁶.

Few studies are available to document the long term developmental outcomes of infants exposed to fever in pregnancy. In the CHARGE (Childhood Autism Risks from Genetics and Environment) study²⁸, mothers of children diagnosed with autism spectrum disorder (ASD)

or developmental delay (DD) were asked retrospectively, 2 – 5 years after their pregnancy, whether or not they had suffered from flu or a fever in pregnancy. Neither ASD nor DD were associated with self-reported influenza in pregnancy. However, both ASD and DD were associated with the report of fever during pregnancy, OR 2.12 (95% CI 1.17-3.84) and OR 2.50 (95% CI 1.20 – 5.20) respectively. The offspring of mothers who took anti-pyretic medications had a lower risk of ASD, OR 1.30 (0.59-2.84) compared with those who did not OR 2.55 (1.30-4.99).

High-dose aspirin and non-steroidal anti-inflammatory agents should be used with caution during the third trimester due to the risk of premature closure of the fetal ductus arteriosus²⁹. Alternative agents should be considered.

Key Points 2:

- Fever may be associated with an increased risk of congenital abnormalities
- Antipyretics such as paracetamol, may be beneficial in reducing adverse pregnancy outcomes

GRADE: LOW QUALITY EVIDENCE

Although most commonly bacterial in etiology, sepsis can also result from viral and other causes (Table 3). A number of non-infective conditions can mimic sepsis and should be

Key Points 3:

- Sepsis-related maternal death is most commonly caused by Group A *Streptococcus*
- E. Coli is the commonest cause of maternal bacterial infection
- Consider non-bacterial and non-infective conditions that may mimic sepsis

GRADE: HIGH QUALITY EVIDENCE

Investigations in sepsis

Obstetric patients with infections may present with nonspecific symptoms and early investigation is necessary to exclude severe infection³⁰. Maternity units should ensure observations are recorded on maternity specific charts for all obstetric and postpartum patients³¹. Utilization of these charts has been shown to promote earlier detection and therefore treatment of pregnant or early post partum women who are developing a critical illness³².

Once infection is suspected, treatment should be commenced and the likely source and severity of sepsis elucidated via history, examination and investigations. Investigations are directed at determining the etiology and risk stratification of sepsis as well as organisation of care for women in the most appropriate clinical area. Sepsis during pregnancy will require maternal investigations as detailed below and fetal wellbeing assessment with cardiotocograph (CTG) and /or ultrasound. Table 5 lists the first line investigations to be undertaken in sepsis, possible changes in sepsis and normal pregnancy reference ranges if different from the non pregnant state. Two important considerations are:

- Two sets of peripheral blood cultures should be taken immediately and sequentially if possible before administration of antibiotics. **Their collection should not delay antibiotic treatment.** Cultures should also be taken from all vascular catheter lines (catheter blood cultures) and any other potential sources of infection. Determining the etiology of the infection will allow for targeting of antimicrobial therapy.
- Arterial blood gases should be undertaken to determine presence of hypoxia, hypercapnea, metabolic state and lactate level. Elevated lactate levels are an indication of tissue hypoperfusion with values greater than 2 mmol/L being associated with increased mortality in pregnancy²⁴. The sampling site does not affect the serum lactate results (eg. arterial, venous or capillary³³). If unable to obtain an arterial lactate, a venous lactate can be collected.

Additional investigations may be required depending on initial investigation results and the likely source of infection. Appropriate imaging should **not** be withheld because a woman is pregnant. Concerns about radiation exposure to her developing fetus or proliferating maternal breast tissue need to be balanced against the clinical need for imaging³⁴.

Key Points 4:

- Maternal observation should be recorded on maternity specific observation charts
- Blood cultures and other specimens should be obtained before antibiotics given:

Treatment in the golden hour

Treatment should be commenced as soon as practical - ideally within the first hour ('golden hour') of sepsis being suspected. Empiric treatment should include fluid resuscitation, correction of hypoxia and antimicrobials (antibiotics or antivirals as appropriate). Source control, consideration of the appropriate area of care as well as venous thromboembolism prophylaxis also need to be considered.

Fluid resuscitation

In most circumstances, the initial treatment of hypotension in sepsis is fluid administration. Fluid resuscitation is vital in sepsis to optimise circulating volume and improve blood pressure and tissue perfusion. The preferred fluid for resuscitation is an isotonic crystalloid (usually 0.9% normal saline). Blood may also be used as fluid replacement if there is evidence of blood loss or severe anaemia. If, despite fluid resuscitation (1-2L), the mean arterial pressure and other indices do not improve, care will need to be escalated. Vasopressors may be required³⁵ see 'Intensive Care Issues' below.

Treatment for bacterial sepsis

When a bacterial source of sepsis in pregnancy or postpartum is suspected, prompt treatment with antibiotics within one hour is critical. Maternal mortality can increase by 8% for each hour's delay in administering antibiotics³⁶. Following principles of antibiotic stewardship recommended in both Australia and New Zealand, selection of antibiotics needs to be

appropriate for the suspected infection, whilst minimizing the risk of adverse effects and reducing the emergence of antibiotic resistance^{37, 38}.

A consultant obstetrician and a physician experienced in the management of sepsis in pregnancy should be involved in the care of a pregnant or postpartum patient from the time of sepsis diagnosis or recognition. However, investigation and treatment should not be delayed while waiting for expert consultation. Once a source of sepsis is identified, source control is a priority and may involve abscess drainage or delivery of the fetus.

When treating immunosuppressed women a physician should be involved in decision making as soon as possible after the diagnosis or recognition of sepsis. This should **not** delay antibiotic treatment. Women may be immunosuppressed with immunomodulators for solid organ transplant, malignancy or autoimmune disease; chronic infection including HIV; or significant medical co-morbidities such as diabetes.

Treatment of sepsis of unknown source

Table 6 summarizes the recommendations for empiric antibiotic treatment. Antibiotic resistance patterns and local practices will vary so it is important to seek local specialist advice as soon as possible. Therapy should be refined as culture and imaging results define the source of sepsis and its culprit organisms. The Australia-wide eTG (electronic antibiotic Therapeutic Guidelines) are available at the following URL: <https://tgldcdp.tg.org.au/guideLine?guidelinePage=Antibiotic&frompage=etgcomplete>

Treatment of sepsis of viral etiology – Influenza

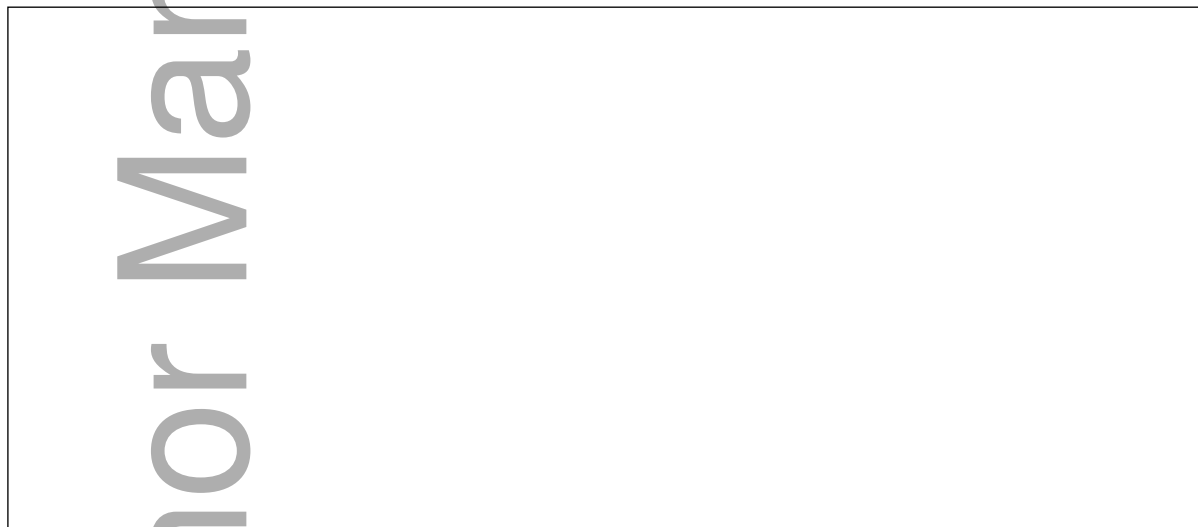
Neuraminidase inhibitors are recommended for the treatment of influenza³⁹. Oseltamivir (treatment dose: 75mg capsule twice daily for 5 days) has more obstetric safety data available than zanamivir and is the agent of choice in pregnancy⁴⁰. There is a low rate of transplacental transfer, estimated at between 1-14% of maternal concentrations in ex vivo perfusion studies⁴¹. In the setting of H1N1 pandemic influenza, early antiviral therapy (initiation < 2 days) in pregnant women was associated with an 84% reduction in admissions to intensive care⁴².

Thromboembolism prophylaxis

Both pregnancy and sepsis are independent risk factors for venous thromboembolism⁴³. Thus prevention of venous thromboembolism is critically important. Unfractionated heparin (UH) and low molecular weight heparin (LMWH) have been used extensively in pregnancy and have been shown in large clinical trials to be effective in the prevention of thromboembolism⁴⁴.

Pharmacological considerations for pregnancy and breastfeeding

While most antibiotics are found in breast milk of a lactating woman, the relative infant dose is generally small. Breastfed infants should be monitored for side effects such as diarrhoea, vomiting, skin rash or thrush while their mothers are being treated with antibiotics. Please refer to the eTG for advice on antibiotic use in breast feeding mothers, URL: <https://tgldcdp.tg.org.au.acs.hcn.com.au/quicklinks?type=Pregnancyandbreastfeeding>.



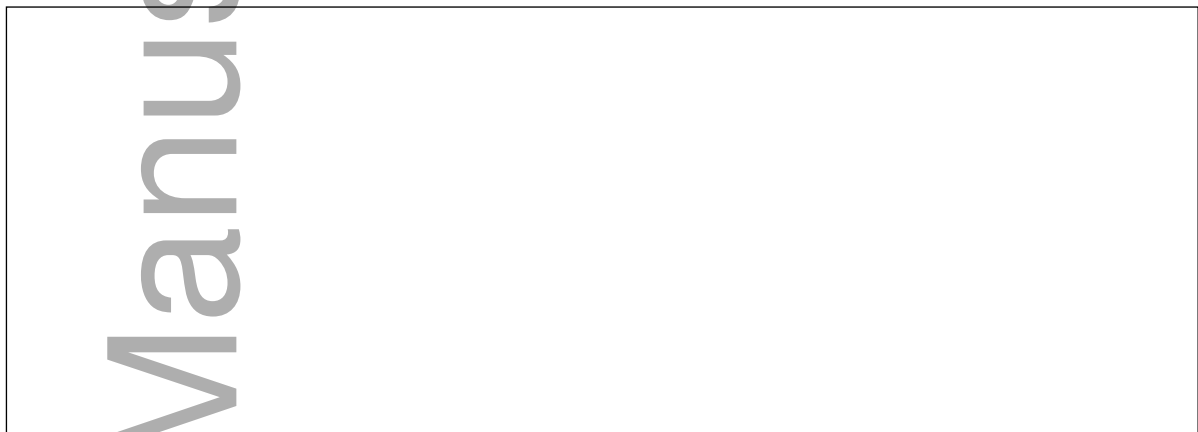
Timing and mode of delivery

The timing of delivery will be determined by a) the presence of intrauterine sepsis, b) the nature of the maternal sepsis and response to initial resuscitation efforts and c) the gestation of the pregnancy and fetal status.

In the setting of intrauterine sepsis, delivery should always be considered regardless of the gestation. Corticosteroids should be considered for fetal lung maturation but this decision needs to be balanced against the urgency of delivery⁴⁵.

Intrauterine sepsis should be suspected in the presence of maternal fever, ruptured membranes or recent intrauterine procedures such as amniocentesis⁴⁶, maternal tachycardia, fetal tachycardia, uterine tenderness or offensive vaginal discharge. While the onset of chorioamnionitis may be non-specific and insidious, rapid deterioration is possible.

In cases of extra-uterine sepsis, efforts to treat maternal sepsis and prolong gestation should be considered at gestations remote from term, although it is reasonable to consider delivery in term pregnancies as a means of improving maternal resuscitation efforts. Fetal wellbeing should be monitored during maternal sepsis with the most gestation appropriate method.



Role of the anesthetist in managing maternal sepsis

The role of the anesthetist in managing maternal sepsis includes:

- initial resuscitation and stabilisation of the patient
- transfer of the sick patient (to imaging or intensive care unit)
- intra-operative care during delivery
- anaesthesia for surgical management of sepsis

Patient transfer

The transport team must be experienced in securing airways, ventilation, resuscitation and other anticipated emergency procedures. A comprehensive hand over should take place at the receiving facility. The responsibility of intra and inter-hospital transfers often rests with the anesthetist to provide the standard of care as set out in The Australian and New Zealand College of Anesthetists professional document, PS52 (2015) Guidelines for Transport of

Critically Ill Patients. These guidelines state, “the level of care provided during transport must aim to at least equal that at the point of referral and must prepare the patient for admission to the receiving services”⁴⁷.

Spinal anaesthesia

Underlying sepsis is a risk factor for infectious complications of regional anaesthesia. The greatest concern is infection around the spine and spinal cord, presenting either as meningitis or cord compression secondary to abscess formation with the potential for permanent neurological deficit. It is difficult to accurately quantify the risk of infection following neuraxial analgesia and anaesthesia due to the great variability in the reported incidence in the literature; from an estimated incidence of spinal/epidural abscess after epidural analgesia of 1 in 1,930 to 1.1 infections per 100,000 neuraxial blocks⁴⁸. However, epidural anaesthesia carries a greater risk of infectious complications than spinal techniques⁴⁹.

Despite the low risk of central nervous system infection, which may potentially occur in any bacteraemic patient, the decision to proceed with neuraxial blockade in a febrile or infected patient must be carefully considered and made on a case by case basis⁵⁰⁻⁵²:

1. Except in the most extraordinary circumstances, central neuronal block should not be performed in patients with untreated systemic infection.
2. Patients with evidence of systemic infection may safely undergo spinal anaesthesia, provided appropriate antibiotic therapy is initiated before dural puncture and the patient has shown a response to therapy; placement of an indwelling epidural or intrathecal catheter remains controversial.
3. Spinal anaesthesia may be safely performed in patients at risk for low grade transient bacteraemia after dural puncture.

General anaesthesia

The septic obstetric patient often exhibits hemodynamic instability and has a greater (than just pregnancy induced) metabolic oxygen demand. In practice, relevant issues for the administration of general anaesthesia include:

- **A – Airway:** Delayed gastric emptying with increased risk of reflux and aspiration. It is recommended that women are premedicated with combination antacid antihistamine prophylaxis, e.g. effervescent ranitidine 150mg. A rapid sequence induction is also recommended.

- **B – Breathing:** Increased metabolic demand leading to accelerated hypoxaemia during periods of apnoea. It is recommended women receive adequate pre-oxygenation prior to anaesthesia induction. There is reduced functional residual capacity with increased ventilation/perfusion mismatch. It is recommended ventilation strategies to maintain oxygenation and minimise further lung injury are employed.
- **C – Circulation:** Maintenance of systemic blood pressure for adequate organ perfusion, including the placental bed. It is recommended to avoid aortocaval compression using a lateral uterine tilt, ensure adequate fluid resuscitation including the appropriate use of blood products and if required, inotropic support. Alpha adrenergic agonists (specifically noradrenaline) are the agents of choice for maintenance of uteroplacental flow.

Key Points 7:

- Neuraxial blocks in women with untreated sepsis are associated with increased complications
- Septic women experience increased haemodynamic instability during anesthesia

GRADE: LOW QUALITY EVIDENCE

Intensive Care Issues

Adequate initial resuscitation and treatment of sepsis may result in stabilisation and prevent progression and deterioration, averting the requirement for intensive care. However, as stated early consideration should be given to establishing the most appropriate venue of care for these women. The indications for ICU admission will vary depending on local resources and expertise. It is preferable that an ICU opinion and /or admission should occur before the development of severe complications such as frank organ failure or catastrophic shock. If any clinical concern exists then escalation of care should be considered early. Table 7 sets out in general terms when an ICU opinion should be obtained and an ICU admission considered.

Key Points 8:

- Liaise with ICU where there is evidence of organ dysfunction, hypotension or cardio respiratory compromise
- Early ICU involvement is preferable and encouraged
- Indications for ICU admission varies based on local resources and experience

GRADE: LOW QUALITY EVIDENCE

Table and Figure Legends

Figure 1: Flowchart for the assessment and management of sepsis in pregnancy. The clinically important steps are noted in blue boxes and comments relating to the steps are in neighboring green boxes.

Table 1: Obstetrically modified qSOFA score

Table 2: Obstetrically modified SOFA score

Table 3: Infectious causes of sepsis in pregnancy and postpartum

Table 4: Non- infectious conditions that can mimic sepsis in pregnancy

Table 5: First line investigations recommended for suspected sepsis

Table 6: Recommendations for antimicrobial treatment of sepsis with unknown source

Table 7: Indications for involvement of ICU

References

- 1 AIHW: Humphrey MD, Chughtai A, Macaldowie A, *et al.* Maternal deaths in Australia 2008–2012. In: AIHW., (ed.). Vol. Maternal deaths series no. 5. Cat. no. PER 70. Canberra; 2015.
- 2 Cantwell R, Clutton-Brock T, Cooper G, *et al.* Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom.[Erratum appears in BJOG. 2015 Apr;122(5):e1]. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2011; **118 Suppl 1**: 1-203.
- 3 Perinatal and Maternal Mortality Review Committee. Ninth Annual Report of the Perinatal and Maternal Mortality Review Committee: Reporting mortality 2013. In: PMMRC, (ed.) Wellington, New Zealand: Health Quality & Safety Commission.; 2015.
- 4 Commission Clinical Excellence. Sepsis Kills; <http://www.cec.health.nsw.gov.au/patient-safety-programs/adult-patient-safety/sepsis-kills/sepsis-tools>, accessed 26 March 2017, 2016.
- 5 Commission Clinical Excellence. Maternal Sepsis Pathway. http://www.cec.health.nsw.gov.au/__data/assets/pdf_file/0008/292193/Maternal-Sepsis-Pathway-December-2016.pdf. Accessed 26th March 2017. 2016.
- 6 Dellinger RP, Levy MM, Rhodes A, *et al.* Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Medicine*. **39**: 165-228.
- 7 Cordioli RL, Cordioli E, Negrini R, *et al.* Sepsis and pregnancy: do we know how to treat this situation? *Revista Brasileira de Terapia Intensiva*. 2013; **25**: 334-44.
- 8 Chau A, Tsen LC. Fetal optimization during maternal sepsis: relevance and response of the obstetric anesthesiologist. *Curr Opin Anaesthesiol*. 2014; **27**: 259-66.
- 9 Mor G, Cardenas, I. Immune response in pregnancy 2010. *Am J Reprod Immunol*. 2010; **63**.
- 10 Shekelle PG, Woolf SH, Eccles M, *et al.* Clinical guidelines: developing guidelines. *BMJ*. **318**: 593-6.
- 11 Jaeschke R, Guyatt GH, Dellinger P, *et al.* Use of GRADE grid to reach decisions on clinical practice guidelines when consensus is elusive. *BMJ*. **337**: a744.
- 12 Singer M, Deutschman CS, Seymour CW, *et al.* The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016; **315**: 801-10.

- 13 Vincent JL, de Mendonca A, Cantraine F, *et al.* Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med.* 1998; **26**: 1793-800.
- 14 Seymour CW, Liu VX, Iwashyna TJ, *et al.* Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA.* 2016; **315**: 762-74.
- 15 Hegewald MJ, Crapo RO. Respiratory physiology in pregnancy. *Clin Chest Med.* 2011; **32**: 1-13, vii.
- 16 Cretikos MA, Bellomo R, Hillman K, *et al.* Respiratory rate: the neglected vital sign. *Med J Aust.* 2008; **188**: 657-9.
- 17 Albright CM, Lopes V, Rouse DJ, *et al.* The Sepsis in Obstetrics Score: a model to identify risk of morbidity from sepsis in pregnancy. *Am J Obstet Gynecol* 2014; **211**: 31-8.
- 18 Macdonald-Wallis C, Silverwood RJ, Fraser A, *et al.* Gestational-age-specific reference ranges for blood pressure in pregnancy: findings from a prospective cohort. *J Hypertens.* 2015; **33**: 96-105.
- 19 Oliveira-Neto A, Parpinelli MA, Cecatti JG, *et al.* Sequential organ failure assessment score for evaluating organ failure and outcome of severe maternal morbidity in obstetric intensive care. *ScientificWorldJournal.* 2012; **2012**: 172145.
- 20 Devabhaktuni P, Samavedam S, Gopal T, *et al.* Clinical profile and outcome of obstetric ICU patients. APACHE II, SOFA, SAPS II and MPM scoring systems for prediction of prognosis. *Open Journal of Obstetrics and Gynecology.* 2013; **3**: 41-50.
- 21 Abbassi-Ghanavati M, Cunningham, FG. Pregnancy and laboratory studies: a reference table for clinicians. *Obstet Gynecol.* 2009; **114**: 1326-31.
- 22 Larsson A, Palm, M, Hansson, L-O *et al.* Reference values for clinical chemistry tests during normal pregnancy. *BJOG: An International Journal of Obstetrics & Gynaecology.* 2008; **115**: 874-81.
- 23 Shankar-Hari M, Phillips GS, Levy ML, *et al.* Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA.* 2016; **315**: 775-87.
- 24 Mohamed-Ahmed O, Nair M, Acosta C, *et al.* Progression from severe sepsis in pregnancy to death: a UK population-based case-control analysis. *BJOG.* 2015; **122**: 1506-15.

- 25 Small E, Clements CM. Defining fever: likelihood of infection diagnosis as a function of body temperature in the emergency department. *Critical Care*. 2014; **18**: P42-P.
- 26 Dreier J, Andersen AM, Berg-Beckhoff G. Systematic Review and Meta-analyses: Fever in Pregnancy and Health Impacts in the Offspring. *Pediatrics and Neonatology*. 2014; **674**: 1-10.
- 27 Edwards M. "Review: Hyperthermia and fever during Pregnancy". *Birth Defects res A Clin Mol Teratol Jul*. 2006 **76**: 507-16.
- 28 Zerbo O, Iosif AN, Walker C *et al*. Is Maternal Influenza or Fever During Pregnancy Associated with Autism or Developmental Delays? Results from the CHARGE (Childhood Autism Risks from Genetics and Environment) Study", . *J Autism Dev Disord*. 2013; **43**: 25-33.
- 29 Koren G, Florescu A, Costei AM, *et al*. Nonsteroidal antiinflammatory drugs during third trimester and the risk of premature closure of the ductus arteriosus: a meta-analysis. *Ann Pharmacother*. 2006; **40**: 824-9.
- 30 AIHW: Johnson S, Li Z, Hilder L, *et al*. Maternal deaths in Australia 2006-2010. In: AIHW, (ed.). Vol. Maternal deaths series no. 4. Cat. no. PER 61. Canberra; 2014.
- 31 Friedman AM. Maternal early warning systems. *Obstet Gynecol Clin North Am*. 2015; **42**: 289-98.
- 32 Knight M, Brocklehurst P, Neilson J, *et al*. (Eds.) on behalf of MRBRRACE-UK. . Saving Lives, Improving Mothers' Care - Lessons learned to inform future maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009-12. Oxford: National Perinatal Epidemiology Unit. *University of Oxford* 2014.
- 33 Bakker J, Nijsten M.W, Jansen TC. Clinical use of lactate monitoring in critically ill patients. *Ann Intensive Care*. 2013; **3**: 1-8.
- 34 Lowe S. Diagnostic Radiography in Pregnancy: Risks and Reality. *Australian and New Zealand Journal of Obstetrics & Gynaecology*. 2004; **44**: 191-6.
- 35 Fernandez-Perez ER, Pendem S and Farmer JC. Sepsis during pregnancy. *Crit Care Med*. 2005; **33**: S286-93.
- 36 Kumar A, Roberts D, Wood KE, *et al*. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006; **34**: 1589-96.
- 37 Australian Commission on Safety and Quality in Health Care. Antimicrobial Stewardship Clinical Care Standard. Sydney:ACSQHC, 2014.

- 38 Thompson I. Antimicrobial stewardship in New Zealand: Scoping research
<http://www.hqsc.govt.nz/assets/Infectionrevention/PR/Antimicrobial-stewardship-report.pdf>; 2013.
- 39 Australian Therapeutic Guidelines:Antibiotic, version.15. Therapeutic Guidelines Limited: NHMRC; 2014.
- 40 World Health Organisation. WHO position paper on influenza vaccines - November 2012. *Weekly epidemiological record*. 2012; **47**: 461-76.
- 41 Beigi RH, Pillai VC, Venkataramanan R, *et al*. Oseltamivir for the treatment of H1N1 influenza during pregnancy. *Clinical pharmacology and therapeutics*. 2015; **98**: 403-5.
- 42 Tomi M, Nishimura T, Nakashima E. Mother-to-fetus transfer of antiviral drugs and the involvement of transporters at the placental barrier. *J Pharm Sci*. 2011; **100**: 3708-18.
- 43 Yates L, Pierce M, Stephens S, *et al*. Influenza A/H1N1v in pregnancy: an investigation of the characteristics and management of affected women and the relationship to pregnancy outcomes for mother and infant. *Health technology assessment (Winchester, England)*. 2010; **14**: 109-82.
- 44 McLintock C BT, Chunilal S, Dekker G, *et al*. Councils of the Society of Obstetric Medicine of A, New Z, Australasian Society of T and Haemostasis. Recommendations for the prevention of pregnancy-associated venous thromboembolism. *The Australian & New Zealand journal of obstetrics & gynaecology*. 2012; **52**: 3-13.
- 45 Bain E WA, Tooher R, Gates S, *et al*. Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period. *Cochrane Database Syst Rev*. 2014; **2**:CD001689.
- 46 Antenatal corticosteroids guidelines. Antenatal corticosteroids given to women prior to birth to improve fetal, infant, child and adult health. *Liggins Institute, the University of Auckland, Auckland. New Zealand*. http://www.ligginsinstitute.org/ANC_CPG/. 2015.
- 47 Greenberg MB, Anderson BL, Schulkin J, *et al*. A first look at chorioamnionitis management practice variation among US obstetricians. *Infect Dis ObstetGynecol* 2012. 2012; **6**: 362.
- 48 Australian and New Zealand College of Anaesthetists. PS52 Guidelines for Transport of Critically Ill Patients: <http://www.anzca.edu.au/documents/ps52-2015-guidelines-for-transport-of-critically-i>; 2015.

- 49 Hebl JR, Niesen AD. Infectious complications of regional anesthesia. *Curr Opin Anaesthesiol.* 2011; **24**: 573-80.
- 50 Cook TM, Counsell D, Wildsmith JA. Major complications of central neuraxial block: report on the Third National Audit Project of the Royal College of Anaesthetists. *Br J Anaesth.* 2009; **102**: 179-90. .
- 51 Dellinger RP, Rhodes A, Annane D, *et al.* Surviving Sepsis Campaign Guidelines Committee including the Pediatric S. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med.* 2013; **41**: 580-637.
- 52 Wedel DJ, Horlocker TT. Regional anesthesia in the febrile or infected patient. . *Reg Anesth Pain Med.* 2006; **31**: 324-33.
- 53 Horlocker TT, Wedel DJ. Infectious complications of regional anesthesia. *Best Pract Res Clin Anaesthesiol.* 2008; **22**: 451-75.

Table 1: Obstetrically modified qSOFA score

Parameter	Score	
	0	1
Systolic Blood Pressure	$\geq 90\text{mmHg}$	$< 90\text{mmHg}$
Respiratory Rate	Less than 25 breaths/min	25 breath/min or greater
Altered mentation	Alert	Not alert

mmHg- Millimetres of mercury, Min- minute

Table 2: Obstetrically modified SOFA score

System Parameter	Score		
	0	1	2
Respiration			
PaO ₂ /FIO ₂	≥400	300 - <400	<300
Coagulation			
Platelets, x10 ⁶ /L	≥150	100-150	<100
Liver			
Bilirubin (μmol/L)	≤20	20-32	>32
Cardiovascular			
Mean Arterial Pressure (mm Hg)	MAP≥70	MAP<70	Vasopressors required
Central Nervous System			
	Alert	Rousable by voice	Rousable by pain
Renal			
Creatinine (μmol/L)	≤90	90-120	>120

MAP- Mean arterial pressure, mmHg – millimetres of mercury, μmol/L- micromoles per litre, PaO₂- partial pressure of oxygen (in mmHg), FIO₂- fraction of inspired oxygen (expressed as a decimal)

Table 3: Infectious causes of sepsis in pregnancy and postpartum

Infection	Pathogens
Bacterial - common	Group A- beta-hemolytic Streptococcus (GAS) pyogenes Escherichia Coli Group B Streptococcus Klebsiella pneumoniae Staphylococcus aureus Streptococcus pneumonia Proteus mirabilis Anaerobic organisms
Bacterial – less common	Haemophilus influenza Listeria monocytogenes Clostridium species MycobacteriumTuberculosis
Viral	Influenza Varicella zoster virus Herpes Simplex virus Cytomegalovirus

Table 4: Non- infectious conditions that can mimic sepsis in pregnancy

Condition	Common Maternal Clinical Features
Acute pulmonary embolism	Hypotension, tachypnoea, tachycardia, low grade fever
Amniotic fluid embolism	Hypotension, tachycardia, haemorrhage
Acute pancreatitis	Fever, nausea, vomiting, abdominal pain
Acute Fatty Liver of Pregnancy	Fatigue, nausea, vomiting, abdominal pain, jaundice, impaired level of consciousness
Adverse drug reactions, drug fever	Hypotension, relative bradycardia, fever, rash, angio-oedema
Acute liver failure-drug related, viral	Jaundice, nausea, vomiting, abdominal pain, impaired level of consciousness
Acute adrenal insufficiency	Weakness, fatigue, nausea, anorexia, weight loss, hypotension, fever
Acute pituitary insufficiency	Failure to lactate, hypotension, relative bradycardia, polyuria, polydipsia
Autoimmune conditions	Low grade fever, rash (eg.malar rash), arthritis, dry eyes or mouth, mouth ulcers, diagnostic serology
Concealed haemorrhage including ectopic pregnancy	Hypotension, tachycardia, low grade fever
Disseminated Malignancy	Low grade fever, weight loss
Pelvic Thrombosis	Pelvic pain, fever,
Transfusion reactions	High fever, rigors, dysrhythmia, tachypnoea, hypotension, rash, bleeding, haematuria

Table 5: First line investigations recommended for suspected sepsis

Investigation ⁵¹	Obstetric reference range (if relevant) ²¹
Blood cultures - At least 2 sets, prior to antibiotic commencement as long as there is no delay. - Obtain samples from different sites - Cultures should also be obtained from IV access devices Other Cultures - Obtain cultures of additional sites as clinically indicated and as soon as possible Eg. urine MCS, wound swab - episiotomy, caesarean, placental swabs, amniotic fluid, sputum culture, naso-pharyngeal aspirate/swab, cerebrospinal fluid, vaginal swabs, stool culture	
Arterial blood gases –detect acidosis, hypoxaemia, lactate as below	PaO₂: <u>1st trimester</u>: 93-100 mmHg, <u>2nd trimester</u>: 90-98mmHg, <u>3rd trimester</u>: 92-107mmHg PaCO₂: 25-33mmHg, Arterial pH: 7.4-7.47, HCO₃ 16-22mmol/L
Lactate elevated levels in sepsis relate to tissue hypoperfusion and are associated with an increased sepsis mortality risk	0.6-1.8 mmol/L
Full blood count	White cell count :6-17 X 10⁹/L (may increase to 9-15 X 10⁹/L immediately post-delivery). Steroids also increase white cell count Platelets – lower limit of normal 150-420 x10⁹/L
Coagulation studies	No change
Creatinine urea and electrolytes Measure at baseline and until the patient improves, elevated creatinine is a sign of severe sepsis	Creatinine Varies with Gestation (reference ranges) :<u>1st trimester</u>:35-62µmol/L, <u>2nd trimester</u>: 35-71µmol/L, <u>3rd trimester</u>: 35-80µmol/L
Liver function tests - Baseline test, may be elevated if sepsis source is from hepatic or perihepatic infections - May be elevated due to septic shock affecting hepatic blood flow and metabolism	AST 3-33 U/L, ALT 2-33 U/L, Alkaline Phosphatase 17-229 U/L GGT 2-26 U/L, Total Bilirubin 1.7-19 µmol/L

CXR

Fetal Assessment – CTG and /or fetal ultrasound

A non-reassuring CTG suggests inadequate uteroplacental perfusion and may reflect maternal organ hypoperfusion or intrauterine sepsis

PaO₂- partial pressure of oxygen (in mmHg), PaCO₂- partial pressure of carbon dioxide (in mmHg), HCO₃⁻ Bicarbonate, IV- intravenous, MCS- microscopy, culture and sensitivity, CTG- cardiotocograph, CXR- Chest x-ray, mmol/L- millimoles per litre, µmol/L- micromoles per litre, AST- aspartate aminotransferase, ALT-alanine aminotransferase, GGT- gamma glutamyl transferase, U/L- units per litre.

	Australian and New Zealand Antibiotic Regimen ³⁹	Alternative for penicillin hypersensitivity [#]
Community-acquired sepsis (source not apparent) ⁺	<u>Aus</u> : amoxicillin/ampicillin 2g IV 6-hourly PLUS gentamicin 4-7mg/kg (first dose) IV* PLUS metronidazole 500mg IV 12-hourly <u>NZ</u>: cefuroxime 1.5g IV 8-hourly PLUS gentamicin 4-7mg/kg (first dose) IV * PLUS metronidazole 500mg IV 12-hourly <u>At risk of MRSA sepsis</u> (based on previous swabs/cultures and local epidemiology): ADD vancomycin 25-30mg/kg (loading dose) IV * <u>At risk of Group A Streptococcal (GAS) sepsis</u>: ADD clindamycin 600mg IV 8-hourly, PLUS consider normal immunoglobulin 1-2g/kg IV, for up to 2 doses during the first 72 hours	Clindamycin 600mg IV 8-hourly PLUS gentamicin 4-7mg/kg (first dose) IV (severe hypersensitivity) Cefazolin 2g IV 6-hourly PLUS gentamicin 4-7mg/kg (first dose) IV* PLUS metronidazole 500mg IV 12-hourly (mild-moderate hypersensitivity)
Hospital-acquired sepsis (source not apparent)	<u>Aus</u>: piperacillin 4 g + tazobactam 0.5g IV 8-hourly AND consider gentamicin 4-7mg/kg (first dose) IV* (if local epidemiology suggests Gram negative aminoglycoside susceptibility) <u>NZ</u>: cefuroxime 1.5g IV 8-hourly PLUS gentamicin 4-7mg/kg (first dose) IV * PLUS metronidazole 500mg IV 12-hourly <u>At risk of MRSA sepsis</u> (based on previous swabs/cultures and local epidemiology or if line sepsis) ADD vancomycin 25-30mg/kg (loading dose) IV *	Severe: ciprofloxacin 400mg IV 8-hourly PLUS vancomycin 25-30mg/kg IV*

At risk of multidrug-resistant Gram-negative organisms: use as a SINGLE AGENT **meropenem** 1g IV 8-hourly

At risk of Group A Streptococcal (GAS) sepsis: ADD **clindamycin** 600mg IV 8-hourly PLUS consider normal immunoglobulin 1-2g/kg IV, for up to 2 doses during the first 72 hours

Consider influenza

Oseltamivir 75mg BD or **Zanamivir** 2 inhalations (each 5mg) twice daily for 5 days

* Use local protocols for gentamicin and vancomycin dosing and monitoring. Once daily dosing of gentamicin in pregnancy and postpartum can be used and in pregnancy results in levels below the toxicity threshold for more hours per day than in 8-hourly dosing. ⁺ NZ regime does not cover listeria – if suspected use a penicillin as per Australian regime. [#] NZ has increasing Group B strep resistance to clindamycin and macrolides – if penicillin hypersensitivity seek expert advice for best agent. IV- intravenous, MRSA- methicillin resistant staphylococcus aureas, mg/kg- milligrams per kilogram, BD- twice daily, mg- milligrams.

Table 6: Recommendations for antimicrobial treatment of sepsis with unknown source

Table 7: Indications for involvement of ICU

Indications for ICU involvement	Signs or observations
Cardiorespiratory compromise	hypotension, circulatory instability, worsening tachypnoea, worsening hypoxia, increasing supplemental oxygen requirements
Evidence of organ dysfunction	altered mental status, oliguria, worsening urea and creatinine, other e.g. coagulation failure, cytopenias, worsening hepatic dysfunction
Other evidence of hypoperfusion	metabolic/lactic acidosis, signs of poor tissue perfusion, signs of inadequate placental perfusion
Other serious clinical concern	

