SOMANZ (Society of Obstetric Medicine Australia and New Zealand) guideline aims 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.

SOMANZ Guidelines for the Investigation and Management of Sepsis in Pregnancy

Society of Obstetric Medicine Australia and New Zealand

SOMANZ GUIDELINES FOR THE INVESTIGATION AND MANAGEMENT OF SEPSIS IN PREGNANCY 2017

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Short Title: SOMANZ Sepsis Guidelines

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List of Tables and figures

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The clinical evidence for this guideline has been analysed by the authors according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system[2, 3]. We have adhered to the three principles of development of valid and usable guidelines: 1) a systematic review of the evidence was undertaken with at least the following searches deployed: Cochrane library, Medline and EMBASE. 2) The authors form a multi-disciplinary team 3) Financial support for administration was provided by the Society of Obstetric Medicine of Australia and New Zealand, none of the authors received any direct financial compensation in donating their time to the development of this guideline.

Abbreviations

AIN	Acute interstitial nephritis
AKI	Acute kidney injury
ALT	Alanine aminotransferase
APTT	Activated Partial Thromboplastin Time
ASD	Autism spectrum disorder
AST	Aspartate aminotransferase
BD	Twice daily
BMI	Body mass index
°C	Degrees Celsius
C/S	Caesarean section
CI	Confidence interval
CMV	Cytomegalovirus
CRP	C-reactive protein
CTG	Cardiotocography
CXR	Chest X-ray
DD	Developmental delay
DILI	Drug induced liver injury
DVT	Deep vein thrombosis
EFM	Electronic fetal monitoring
EGDT	Early goal-directed therapy
ESBL	Extended spectrum beta lactamase producers
eTG	Electronic therapeutic guidelines
Fi02	Fraction of inspired oxygen
GAS	Group A streptococcus
GBS	Group B Streptococcus
GCS	Glasgow coma score
GGT	Gamma-glutamyl transferase
GRADE	Grading of recommendations assessment, development and evaluation
Hb	Haemoglobin
HCW	Health care worker
HIV	Human immunodeficiency virus
HR	Heart rate
HSV	Herpes simplex virus
ICU	Intensive care unit
INR	International Normalised Ratio
IV	Intravenous
kg	Kilogram
L	Litre
LMWH	Low molecular heparin
MAP	Mean arterial pressure
MCS	Microscopy, culture and sensitivity
mg	Milligrams
mL	Millilitres
mmHg	millimetres of mercury

mmol/L	Millimoles per litre
MRSA	Methicillin resistant Staphylococcus aureus
NSW	New South Wales
OR	Odds ratio
Pa02	Partial pressure of oxygen
PPROM	Preterm premature rupture of membranes
qSOFA	Quick sepsis-related organ failure
RR	Respiratory rate
SIRS	Systemic inflammatory response syndrome
SOFA	Sepsis-related organ failure
SOMANZ	Society of Obstetric Medicine Australia and New Zealand
TB	Tuberculosis
TIN	Tubulo-interstitial nephritis
™	Trademark
TNFα	Tumour necrosis factor alpha
UH	Unfractionated heparin
UK	United Kingdom
U/L	Units per litre
µmol/L	Micromoles per litre
WCC	White cell count

Summary of recommendations and audit points for implementation

This clinical guideline addresses the issue of sepsis in the peri-partum period. It contains a number of recommendations to guide clinical practice and improve patient outcomes. We have identified several key outcomes that can be audited allowing individual centres to assess their performance in implementation of these guidelines.

Assessment of sepsis

Numerous measures can be used to screen for sepsis. In addition, assessment for end organ dysfunction should be undertaken. Consideration needs to be given to the altered physiology of pregnancy.

- Screen for sepsis using the omqSOFA: respiratory rate ≥25min, mental status (any non-alert state) and systolic blood pressure <90mmHg.
- Assess for any evidence of end organ dysfunction by reviewing for signs such as oliguria or by using omSOFA (increase ≥2)
- Septic shock is a complication of sepsis and is diagnosed when, despite adequate fluid resuscitation, there is hypotension and a requirement for vasopressors. It is associated with an elevated serum lactate and has increased mortality.

[*GRADE: MODERATE QUALITY EVIDENCE]*

Measure of implementation

What is the Incidence of sepsis as a proportion of all births?
What proportion of patients diagnosed with sepsis where screened using qSOFA?

Fever in pregnancy

Although fever is not a part of the new sepsis definitions - it is still an important consideration for pregnant women.

- Fever in the embryonic period of pregnancy may be associated with neural tube defects, oral clefts and congenital heart anomalies.
- Anti-pyretics have a beneficial effect in reducing adverse pregnancy outcomes for women experiencing fever in pregnancy.

[*GRADE: LOW QUALITY EVIDENCE]*

Measure of implementation

What proportion of pregnant women presenting with fever were administered anti-pyretics?

Etiology of sepsis

The etiology of sepsis can be bacterial, viral or non- infective.

- Maternal death from sepsis is most commonly caused by Group A streptococcal infection
- *E. Coli* is the commonest cause of maternal bacterial infection
- Always consider that non-bacterial or non-infective conditions may mimic sepsis.

[*GRADE: HIGH QUALITY EVIDENCE]*

Measure of implementation

What is the prevalence of the different microorganisms causing sepsis?
What proportion of all infections are caused by GAS?

Investigations in sepsis

The type of investigations undertaken to establish the cause of sepsis are important. However, what is more important is that they occur in a timely manner.

- Blood cultures and appropriate microbiological specimens should be obtained ideally prior to commencement of antimicrobial therapy; however this should NOT delay administration of antibiotics or antivirals.
- Imaging should not be withheld just because the patient is pregnant or breast feeding
- Be aware of pregnancy-appropriate normal ranges for investigations and observations

[GRADE: HIGH QUALITY EVIDENCE]

Measure of implementation

What proportion of women with sepsis had blood cultures taken?

Treatment in the golden hour

- All women with suspected sepsis require prompt treatment, ideally within the first hour of presentation.
- Commence fluid resuscitation immediately to stabilize the mother.
- Administer empiric therapy immediately and preferably within one hour
- Where the source of sepsis is identified, de-escalate to appropriate antibiotics
- Consider the impact of the antibiotics on pregnancy and breast feeding

[GRADE: MODERATE QUALITY EVIDENCE]

Measure of implementation

What proportion of women were administered intravenous fluids within the first hour of the suspicion of sepsis?
What proportion of women with sepsis were administered empiric antibiotics within the first hour?

Fetal surveillance

It is important to consider the well-being of the fetus whilst treating the woman with sepsis.

- Consider the most appropriate method of monitoring fetal well-being during maternal sepsis. eg cardiotocography, Doppler heart rate monitoring, ultrasound
- If preterm delivery is required, corticosteroids should be considered for fetal indications. Sepsis is not a contra-indication to steroids
- The onset of chorioamnionitis may be non-specific or insidious, but rapid deterioration is common. Chorioamnionitis requires urgent delivery on both maternal and fetal grounds
- Preterm delivery may be required for either maternal or fetal indications.

[GRADE: MODERATE QUALITY EVIDENCE]

Measure of implementation

What proportion of fetuses of a suitable gestation (greater than 24 weeks) were assessed with electronic fetal monitoring whilst treating the woman with sepsis? (Local practices will determine the lower limit of the gestation at which electronic fetal monitoring should be instigated)

Roles of the anesthetist in managing maternal sepsis

Anesthetists have an important role in caring for women with sepsis - including accessing prompt vascular access for treatment. Further anaesthetic considerations are:

- Neuraxial blocks in women with untreated sepsis may be undertaken only after careful assessment, taking into consideration the increased risk of complications in the short and long term.
- Pregnant women with sepsis experience increased hemodynamic instability during general anesthesia
- Anesthesia during pregnancy in a woman with sepsis does not increase mortality but may be associated with other adverse obstetric events.

[GRADE: LOW QUALITY EVIDENCE]

Measure of implementation

What proportion of pregnant women with sepsis undergo anaesthetic consultation?
What proportion of pregnant women with sepsis, having received neuraxial blockade develop complications, in particular hemodynamic and neurological complications?

Intensive care issues

Intensive care support may be required for women with severe sepsis.

- Liaise with intensive care if the patient has cardiorespiratory compromise (including tachypnea/hypoxia), evidence of end organ dysfunction or hypoperfusion.
- Admit to ICU when:
    - Despite adequate fluid resuscitation there is ongoing hypotension with evidence of systemic hypoperfusion (eg an elevated lactate)
    - Organ supports such as ventilation or circulatory support are being considered
- There is a paucity of data regarding the resuscitation of pregnant women in the intensive care unit. The preferred fluid is an isotonic crystalloid.

[GRADE: LOW QUALITY EVIDENCE]

Measure of implementation

What proportion of women with sepsis required intensive care admission?

What proportion of women with sepsis who had evidence of end-organ dysfunction were referred to intensive care?

1. Introduction

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 2008-2012 [4]. In the period 2008-2012, sepsis accounted for 11.4% of maternal deaths in Australia[4]. 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 UK[5]. Sepsis continues to be one of the major causes of maternal mortality among Aboriginal and Torres Strait Islander women[4]. The ninth Perinatal and Maternal Mortality Review Committee report on maternal deaths in NZ [6] between 2006-2013 indicates 50% of deaths from sepsis were related to Group A streptococcus.

In the UK, sepsis is now the most common cause of direct maternal death. The Confidential Enquiry into Maternal Mortality and Morbidity: Saving Lives, Improving Mothers' Care published in December 2014 included "think sepsis" in its key messages; given that one quarter of women who died had sepsis[7]. Rapid recognition, early antimicrobials and involvement of senior staff are essential factors to improving outcomes. Vague symptoms followed by sudden collapse characterized many of the deaths from sepsis in all reporting countries [5]. In Australia, the Clinical Excellence Commission developed the "Sepsis Kills" program to reduce poor outcomes from sepsis by improving recognition and management [8]. A specific maternal pathway was created [9].

Sepsis can arise at any time during the antepartum, intrapartum and postpartum periods and is often associated with a delay in diagnosis. A number of factors contribute to this including the normal physiological changes of pregnancy that may mask early signs of sepsis [10, 11]. Management plans need to consider the altered immunological response in the parturient [12]. Early recognition and timely treatment by an experienced team is essential in the clinical management of sepsis in the obstetric patient.

The parturient also 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-regulated [13]. Thus any maternal cardiovascular insufficiency may result in compromised fetal perfusion.

2. Definition of sepsis in pregnancy

KEY POINTS

- ***Screen for sepsis using the omqSOFA (respiratory rate ≥25/min, mental status (any non-alert state) and systolic blood pressure <90mmHg)***
- ***Screen for sepsis using clinical parameters including RR, mental status, SBP, pulse and fever. Sepsis may be present with or without fever or an obvious source.***
- ***Assess for evidence of end organ dysfunction using omSOFA (increase ≥2)***
- ***Septic shock is a complication of sepsis and is diagnosed when, despite adequate fluid resuscitation, there is hypotension and a requirement for vasopressors. It is associated with an elevated serum lactate and has increased mortality.***

GRADE EVIDENCE: MODERATE QUALITY

The definition of sepsis has evolved over time and this is in part due to it being a syndrome rather than a specific illness. Despite significant advances, the pathobiology of sepsis remains incomplete and currently no gold standard diagnostic test exists.

Sepsis is broadly defined as life-threatening organ dysfunction caused by a dysregulated host response to infection[14]. It is this dysregulated response and subsequent organ dysfunction that differentiates sepsis from infection. Sepsis can occur at any time during pregnancy or in the early postpartum period. The clinical signs may be insidious until they become overwhelming. Therefore early detection of sepsis is essential to allow for appropriate multidisciplinary management to ensure the best outcomes for the mother and her baby. Septic patients can progress to develop septic shock.

Septic shock is defined as a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities substantially increase mortality[14].

2.1 Sepsis

Sepsis had previously been defined by a set of Systemic Inflammatory Response Syndrome (SIRS) criteria[15]. These criteria, which include pyrexia or hypothermia, increased heart rate and elevated white cell count, are signs that will continue to have a role in the general diagnosis of infection as opposed to the diagnosis of sepsis. The SIRS may only be reflective of an appropriate adaptive host response[14]. The clinical presentation of sepsis can be altered by other preexisting comorbidities, illnesses and therapies. Thus we recommend considering sepsis in any patient with these clinical signs; including fever, increased respiratory rate, hypotension, tachycardia and altered mentation. Other combinations of clinical and biochemical parameters have been shown to better identify infected patients more likely to have sepsis.

Many scores have previously been developed to assist in the identification of those patients who have organ dysfunction caused by an abnormal host response to infection. One of these scores, the SOFA (Sequential (sepsis related) Organ Failure Assessment) score has been shown to reliably identify those patients with a suspected infection who have a

greater morbidity and mortality[16] (Appendix 1). The elements involved in assessing organ dysfunction for the SOFA score are: coagulation, platelet count, liver function (bilirubin), cardiovascular system (mean arterial pressure (MAP) or presence and dose of inotropes and or vasopressors), neurological system (Glasgow Coma Scale: GCS), renal function (creatinine and urine output) and respiration (partial pressure of arterial oxygen(PaO_2)/ fraction of inspired oxygen(FIO_2)) [1, 17]. Each parameter is scored from 0 to 4 – employing the worst available result for the day of assessment. In the peri-partum woman, the parameters of the SOFA must be adjusted to account for the physiological alterations of pregnancy.

2.2 SOMANZ definition of sepsis

Recognising the patient has sepsis is paramount and the first step in appropriate assessment and management. The clinical steps involved in the assessment and management of sepsis in pregnancy have been summarised in a flow chart (Appendix 2). Furthermore, a checklist has also been developed to facilitate clinicians in completing all the actions required (Appendix 2).

For screening for sepsis in clinical use, we recommend the obstetrically modified qSOFA (omqSOFA) (Table 2.1). The full SOFA score should be used for a subsequent, more thorough, assessment.

Table 2.1: Obstetrically modified qSOFA score

Parameter	Score	
	0	1
Systolic Blood Pressure	≥90mmHg	‹90mmHg
Respiratory Rate	Less than 25 breaths/min	25 breath/min or greater
Altered mentation	Alert	Not alert

2.2.1 Obstetrically modified quick SOFA (omqSOFA) score

The qSOFA (quick SOFA- Appendix 3), has been described to screen patients likely to have sepsis in a timely manner[16]. It has been derived from the more complex SOFA score (Appendix 1). The qSOFA requires only clinical data for assessment and can thus be performed quickly without waiting for the results of biochemical or laboratory assessments. 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 mortality [16]. 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 which half were male. Extrapolation to pregnant and postpartum women should be undertaken with caution.

A woman's gravid state will significantly impact several of the variables in the qSOFA. Pregnancy significantly affects systolic blood pressure but not respiratory rate [18] nor mentation. During pregnancy, although women develop a respiratory alkalosis and

compensatory metabolic acidosis there is no increase in normal respiratory rate [18]. Systolic blood pressure usually decreases by 5-10mmHg in pregnancy[19]. 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 outcomes[20].

Given these changes, several modifications are suggested to the qSOFA criteria when applied to pregnancy (omqSOFA- Obstetrically modified qSOFA). Using the omqSOFA (Table 2.1), 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). Glasgow coma scores are not typically formally assessed as part of routine observations in obstetric wards.

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 practice [21].

2.2.2 SOFA

If sepsis is suspected based on screening, then assessment for end-organ dysfunction should be undertaken [14]. This has been defined as an acute change in the total SOFA score of $\geq$2 points consequent to the 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 $\geq$2 is associated with an overall mortality of 10%, however this data is yet to be validated in the obstetric population. The SOFA score has been found to be significantly higher in pregnant women who have died compared to those who have survived in an intensive care setting [22, 23], however the SOFA score has not undergone appropriate 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.

We recommend several modifications when applying the SOFA score to pregnancy (obstetrically modified SOFA- omSOFA) as indicated (Table 2.2):

- In order to demonstrate evidence of end organ dysfunction a score of $\geq$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 35-80µmol/L[24]. Accurate assessment of renal function may be performed using 24 hour urinary creatinine or inulin clearance [25], however these are impractical in the acute setting. For practical purposes, the serum creatinine cut off for the scores of 0, 1 or 2 have been adjusted to <90µmol/L, 90-120µmol/L or greater than 120µmol/L respectively[26]. Estimated glomerular filtration rate (eGFR) is not currently a component of the current definition for organ dysfunction.
- As the GCS is not routinely assessed on maternity wards, the central nervous system category has been changed to reflect the maternal observation chart. Alert will be

scored 0, rousable by voice as 1 and rousable only by pain as 2. Any score other than 0 or alert will 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.

Table 2.2: Obstetrically modified SOFA score (omSOFA)

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

2.3 Septic shock

If sepsis progresses, septic shock may develop, in which underlying circulatory and cellular metabolic abnormalities are profound enough to substantially increase mortality compared to sepsis alone[27]. The clinical criteria validated to identify these 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 resuscitation[28]

No alterations have been made to these definitions for pregnancy.

All women who are being assessed for sepsis should be monitored on the appropriate maternity early warning observation chart [29]. Physiologically, a woman's gravid state means that the cut-offs for clinically significant changes vary significantly compared to non-pregnant patients. Importantly, C-reactive protein (CRP) and fever have not been included in the current definition. They lack sensitivity and are highly variable in pregnancy and should not be used to define or diagnose sepsis [24, 30].

2.4 Postpartum

The postpartum period is defined as birth till 6 weeks after the time of birth. After birth, changes in maternal physiology gradually return to pre-pregnancy levels. Studies have shown these changes occur over a period of weeks to months postpartum [31, 32] Exactly

when each parameter returns to normal is unclear and will vary between individuals. It is important to note systolic and diastolic blood pressures often peak 48 hours after birth and at this time are higher than values obtained six months postpartum [32]

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. The Royal College of Obstetricians and Gynaecologists has specifically defined sepsis in the postpartum period [33]

3. Fever in pregnancy

KEY POINTS

- ***Fever in the embryonic period of pregnancy can be associated with neural tube defects, oral clefts and congenital heart anomalies***
- ***Anti-pyretics have a beneficial effect reducing adverse pregnancy outcomes for women experiencing fever in pregnancy***

GRADE EVIDENCE: LOW QUALITY

3.1 Thermoregulation and mechanisms of fever

The human body temperature is carefully regulated to be maintained between 36.5°C and 37.5°C in order to protect the delicate balance of cellular mechanisms regulating homeostasis. Thermo-regulation is governed by the hypothalamus and interfered with by pyrogenic cytokines, most commonly produced during infection[34].

Pyrogenic cytokines such as interleukin 1 and 6 and tumour necrosis factor alpha (TNFα) act on the hypothalamus and increase maternal body temperature[35]. This interrupts protein synthesis and enzyme production, creating an alteration in cellular processes such as proliferation, migration and apoptosis[36]. This becomes particularly relevant in pregnancy during embryogenesis, when survival is achieved at the expense of normal development via the heat shock response. The febrile response activates the innate immune system and improves the body's response to infection. Various negative feedback systems exist to ensure the hyperthermic response is controlled. Fever increases the body's metabolic rate by up to six-fold thus speeding up the process of eliminating the body of pathogens [37]. Fever in itself, (within a certain temperature range), can therefore be considered a valuable part of the human response to infection. A fever above 40°C however can have direct effects upon key cellular processes, hence the dangers of malignant hyperthermia [36].

The phenomena of heat shock response is a survival response so the organism may survive thermal stress, however this may occur at the expense of cellular damage. Heat shock proteins are produced to enhance cellular resistance to the thermal stress: chaperone proteins adhere to hydrophobic sites on newly synthesised proteins to prevent the formation of functionless aggregates and therefore cell death [38].

This response can occur at any gestation in the pregnancy, however, there are differing potential effects based on the gestation at which the heat shock response occurs (in particular neural tube defects). Later in pregnancy, the effect of heat shock response may be more teratogenic to certain organs or circulations, in particular the fetal brain. Various reports have documented an association between mothers who have suffered from a fever, usually from a suspected viral illness and an increased incidence of cerebral palsy [39-41]. It is unclear however, whether the virus itself or the fever is associated with the brain injury.

3.2 Hyperthermia as a teratogen

3.2.1. During embryogenesis

When the heat shock response is initiated at crucial points during embryogenesis, it can take precedence over other cellular activities such as protein synthesis and cell proliferation which can harm the developing fetus. Animal studies have demonstrated vulnerable periods during organogenesis when fever can be teratogenic: in particular around 4 to 5 weeks of gestation appears critical[36]. An animal embryo must be exposed to a certain level of heat for a certain duration to cause teratogenesis. In rats and guinea pigs this appears to be at least 2 – 2.5^{o}C above normal maternal temperature. The lower the elevation in temperature; the longer is the interval of exposure necessary to cause teratogenesis[36, 38].

The most commonly recorded teratogenic effects of fever from animal studies are neural tube defects, microphthalmia, microcephaly and neurogenic contractures. There is a weaker association with oral cleft and congenital heart disease[38]. Studying fever in human pregnancy is methodologically very difficult and largely reliant upon retrospective case-control or population studies. In a comprehensive systematic review and meta-analysis of fever in human pregnancy and the health impacts on the offspring, Dreier and colleagues [42] 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 early fever (OR 1.94, 95% CI 1.35-2.79) and congenital heart defects were weakly associated with early maternal fever (OR 1.54, 95% CI 1.37-1.74).

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^{o}C was documented there was a greater risk of teratogenic outcome[38]. In human studies, reliance on self-reported temperature may lead to inaccurate results [42].

3.2.2 Later in pregnancy: fever and fetal death, pre-term labour, fetal growth restriction

In the systematic review by Dreier and colleagues [42] no effect of maternal fever was seen on the risk of miscarriage, stillbirth or preterm labour. This may be because recruitment to studies may be too late for women experiencing spontaneous miscarriage early in pregnancy. Whilst there appears to be no direct link between fever and the incidence of pre-term labour, it is well documented that infection – particularly asymptomatic infection of the urinary tract is linked with an increased risk of miscarriage and pre-term labour [43].

3.2.3 Long term neuro-developmental outcome: cerebral palsy, autism

Few studies are available to document the long term developmental outcomes of fever in pregnancy. In the CHARGE (Childhood Autism Risks from Genetics and Environment) study[44], 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. Further, 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). It is possible cytokines produced in response to fever alter the release of neurotransmitters resulting in decreasing cerebral cortical neuronal survival during brain development. However, the risk of recall bias limits the interpretation of these findings.

3.3 Anti-pyretic use: is it beneficial to pregnancy outcome?

Dreier's systematic review[42] included 10 studies of the use of anti-pyretics and pregnancy outcome. The majority of studies reported a positive effect of the use of anti-pyretics in women suffering from fever during pregnancy, with an attenuation of the risk of neural tube defect, oral cleft and congenital heart disease. Aspirin and paracetamol are commonly taken through pregnancy and this systematic review seems to indicate that their use, across several populations is safe in pregnancy.

These benefits need to be balanced with other evidence of potential harm of antipyretics. A recent prospective study of more than 8,000 women[45] indicated a slight increase in behavioural difficulties in children of women who had taken paracetamol through their pregnancy. Paracetamol usage at 18 weeks gestation was associated with a slight increase in conduct problems (OR 1.18 (1.03-1.36) and hyperactivity symptoms (OR 1.21 (1.06-1.38)). These results were similar for women taking paracetamol at 32 weeks. No behavioural problems were associated with maternal post-natal paracetamol usage. There were several limitations of the study including a lack of information about the maternal indication of the paracetamol usage and the dose or length of exposure to paracetamol. Exposure to paracetamol and behavioural outcomes were ascertained by maternal recall that may also have confounded the results. No specific information was collected about maternal fever during the pregnancy. Given the previously documented benefits of anti-pyretics the authors of the current guideline think their continuing use is of greater benefit than harm.

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 arteriosus[46] . Alternative agents should be considered.

4. Etiology of sepsis

KEY POINTS

- ***The commonest cause of maternal death from sepsis is infection with Group A streptococcus species***
- ***E.Coli is the commonest cause of maternal bacterial infection***
- ***Always consider that non-bacterial or non-infective conditions may mimic sepsis***

GRADE EVIDENCE: HIGH QUALITY

Although most commonly bacterial in etiology, sepsis can also result from viral and other causes (Table 4.1). A number of non-infective conditions can mimic clinical sepsis and should be considered by clinicians.

Table 4.1: 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 mirabilus Anaerobic organisms
Bacterial –less common	Haemophilus influenza Listeria monocytogenes Clostridium species MycobacteriumTuberculosis
Viral	Influenza Varicella zoster virus Herpes Simplex virus Cytomegalovirus

4.1 Common bacterial pathogens

4.1.1 Group A beta-hemolytic streptococcus (*Streptococcus pyogenes*)

The most common organism causing maternal mortality from sepsis is Group A beta-hemolytic streptococcus (GAS) [5]. Pregnant and postpartum women have a 20-fold increase in the incidence of invasive group A streptococcal (GAS) infection compared with non-pregnant women [47]. The reasons for the increased incidence of invasive GAS and GBS disease among postpartum women are not clear.

Group A streptococcus is typically found in the community with 5–30% of the population being asymptomatic carriers of the bacteria on the skin or in the throat. It is easily spread by

person to person contact or by droplets. Group A streptococcus can also cause serious illness such as rheumatic fever, scarlet fever, bacteraemia, streptococcal shock syndrome and necrotising fasciitis. In pregnancy and the postpartum period GAS sepsis can present with non-specific symptoms such as fever, sore throat or vomiting and diarrhoea [33]. GAS is very contagious and consideration must be given to prophylaxis of the newborn if this infection occurs peri-partum. At minimum, the team treating the neonate should be notified of this maternal infection. Historically it is the classic organism associated with puerperal sepsis and was a common cause of maternal mortality before antiseptic practice was introduced. Consider a woman at potential risk of GAS sepsis if she is in the postpartum phase, has had recent contact with GAS infection such as bacterial tonsillitis, or culture results suggest Gram positive cocci.

4.1.2 Escherichia coli

E. coli is the most common cause of bacterial infection in pregnancy [48, 49] and is the second most common cause of maternal death due to sepsis [5]. It is the predominant bacteria causing infections in the urinary and genital tracts. In a large series of acute antepartum pyelonephritis *E. coli* was the infectious agent in 70% [50]. *E. coli* sepsis was the cause of 5 maternal deaths in the United Kingdom in the triennium 2006-2008[5].

4.1.3 Group B streptococcus (*Streptococcus agalactiae*)

Group B Streptococcus (GBS) frequently colonises the lower genital and gastro-intestinal tracts. It is an important cause of infection in both mother and infant. Maternal colonisation rates of GBS in pregnancy in Australia vary from 10-30% [51]. An Australian study found a 25% incidence of GBS carriage in women with pre-labour rupture of membranes at term [52]. GBS is a frequent cause of asymptomatic bacteriuria, urinary tract infection, upper genital tract infection, intra-amniotic infection, chorioamnionitis, endometritis and bacteraemia [48, 49]. It is the second most frequent cause of acute antepartum pyelonephritis [50] and may lead to bacteraemia without an obvious focus.

4.1.4 Klebsiella pneumoniae

Klebsiella pneumoniae is typically a nosocomial pathogen but can cause pneumonia, bacteraemia and urinary tract infection. Community acquired infections are less common and it is a less common cause of urinary tract sepsis than *E. coli* [48, 50]. Community acquired infections usually occur in cases with underlying chronic disease such as pulmonary disease, diabetes or alcoholism.

4.1.5 Staphylococcus aureus

Staphylococcus aureus colonises the skin and mucous membranes. It is a common cause of surgical wound infection and mastitis in the postpartum period [48]. The risk of surgical wound infection may be as high as 26.8% in women with a body mass index (BMI) of >45 [53]. Methicillin-resistant *Staphylococcus aureus* (MRSA) is increasing in prevalence in the Australian community. MRSA now accounts for 20% of all staphylococcous aureas bacteraemia[54].

4.1.6 Streptococcus pneumoniae

Streptococcus pneumoniae is a common bacterial cause of community acquired pneumonia and can affect all age groups. Postpartum women have an increased rate of *S. pneumoniae* infection compared to non-pregnant women [55].

4.1.7 Anaerobic infections

Anaerobic infections are often polymicrobial caused by both anaerobic Gram-negative and Gram-positive organisms. The more common anaerobic organisms causing infections are *Bacteroides* sp., *Prevotella* sp., *Prophyromonas* sp., *Peptostreptococcus* sp. and *Finegoldia* sp. These can occur at any stage of pregnancy but are more common in the postpartum period, especially after caesarean section [48, 49]. They can be the causative agents in pelvic infection, endometritis, wound sepsis and rarely necrotizing fasciitis.

4.2 Less common bacterial pathogens

4.2.1 Haemophilus influenzae

H. influenzae is a Gram negative coccobacillus that frequently causes non-invasive upper respiratory tract infections in children and older adults. It is a far less common cause of infection following the introduction of the Hib vaccine. It can colonise the female reproductive tract and cause pelvic inflammatory disease. In pregnancy invasive *H. influenzae* disease presents with bacteraemia, pneumonia and rarely meningitis [56]. Eighty four per cent of infections in pregnancy by H. influenza are un-encapsulated forms with the remaining encapsulated forms being serotypes b, e and f [56].

4.2.2 Listeria monocytogenes

Listeria monocytogenes is a gram positive bacillus which causes infection following ingestion of contaminated food. It is generally contracted from processed ready to eat meats, unpasteurised cheeses, unpasteurised milk, and seafood [57, 58].It is very rare in Australia, with an overall incidence of 0.3 per 100,000 of the population. Materno-fetal infections declined from 2002 to 2003 and the age specific rate of infection in the 20-39 age group is only 0.1 per 100,000 [58]. Studies have suggested 20% of cases involve neonatal infection [57].

The presentation of listeriosis in pregnancy is often non-specific with fever, flu-like symptoms, headache, vomiting and diarrhoea. The placenta can become infected and can provide a reservoir for re-infection. It is associated with spontaneous miscarriage, stillbirth and preterm birth [57]. While maternal illness may be mild, neonatal illness is often severe and can be fatal. Disease in the neonate can be early onset, associated with chorioamnionitis and preterm birth, or late onset occurring between five days and two weeks postpartum, typically in term neonates [57]. Diagnosis of neonatal listeriosis is important as antibiotic therapy can improve outcomes.

4.2.3 Tuberculosis

Worldwide, tuberculosis is one of the leading non obstetric causes of maternal mortality and is the third cause of death for women aged 15-44 [58-60]. Tuberculosis can be more difficult to diagnose in pregnancy because symptoms such as fatigue, shortness of breath, sweats and tiredness are similar to physiological symptoms of pregnancy. Furthermore, pregnancy suppresses the T-helper 1 (Th1) pro-inflammatory response which can mask symptoms while increasing susceptibility to new infection and reactivation of tuberculosis [61]. Early postpartum women are twice as likely to develop tuberculosis as non-pregnant

women [61]. Although congenital tuberculosis appears rare, tuberculosis can be transmitted to the infant through hematogenous spread, aspiration of amniotic fluid during delivery, or respiratory droplets postpartum [61].

In Australia the incidence rate of tuberculosis notifications is 5.5-5.8 per 100,000 population, and is highest in the overseas-born population at 18.4-19.5 per 100,000. The rates in the Australian-born Indigenous population are 4.6 per 100,000 compared to only 0.8 per 100,000 in the Australian-born non-Indigenous population [62]. Only a small number of cases in Australia are multidrug resistant TB and these usually occur in overseas born individuals [62]. In New Zealand the incidence rate of tuberculosis notifications is 6.7 per 100,000 population, and similar to Australia[63], it is highest in the overseas-born population with the Asian ethnic group having a rate of 34.1 per 100,000. The rate for Maori was 5.3 per 100,000 and for Pacific peoples 16.9 per 100,000.

4.3 Viral pathogens

Global influenza pandemics highlight the unique vulnerability of pregnant women to viral illness and viral sepsis. Commonly occurring viruses (location dependant) include influenza, varicella, herpes simplex, cytomegalovirus (CMV) and HIV.

4.3.1 Influenza

Pregnant women are more at risk of developing respiratory complications of influenza, with increased rates of hospital admission and increased mortality compared to the non-pregnant population [64]. Both seasonal and pandemic influenza are associated with increased morbidity and mortality in pregnancy [65].

In NSW Australia, during the 2009 influenza pandemic the rate of respiratory intensive care admission during pregnancy was 14.4 per 100,000 (95% CI 12.5 to 16.2) and in 2007 a non-pandemic year: admissions to intensive care during pregnancy were 8.5 per 100,000 (95% CI 7.0 to 9.9) [66]. During 2009 seven deaths were reported as a result of H1N1 influenza in pregnant or postpartum women who were admitted to ICU for confirmed infection [67]. In non-pandemic years, hospital admission rates for pregnant women with influenza have been estimated as similar to the rate of admission for the elderly (65-69 years), with 1 in 1000 healthy pregnant women hospitalized in a Canadian retrospective cohort study [68]. In Australian data from 2013, the Influenza Complications Alert Network, a sentinel hospital based surveillance program reported 4.3% of hospital admissions were pregnant women. In that cohort, pregnancy was negatively associated with ICU admission (OR 0.20 (0.04, 0.89), P=0.034) [69] .

4.3.2 Varicella

Varicella-zoster virus (VZV) is a highly contagious member of the herpesvirus family, and causes both varicella (chickenpox) and herpes zoster (shingles). Varicella is usually a self-limiting condition that involves the development of a rash approximately 14-16 days post exposure. The rash is initially erythematous macules evolving to produce vesicles which then crust over the subsequent 46-48 hours. The rash is usually accompanied by fever, malaise, anorexia and headache. Varicella can be associated with severe complications, for example encephalitis, cerebellar ataxia and pneumonia/pneumonitis.

Historically the incidence of varicella was estimated at 1-5/10,000 pregnancies, with maternal pneumonia reported to complicate approximately 20% [70] with a mortality rate of approximately 40%. A recent large cohort study examining 7.7 million pregnancy admissions in the USA from 2003-2010 reported a varicella incidence of 1.21/10000, with an incidence of pneumonia of 2.5% and no maternal deaths [71]. In those women with pneumonia, 13% had ARDS/acute respiratory failure, 13% required ventilation and 4.4% had severe sepsis.

Infant complications related to maternal disease will depend on gestational age of exposure. Multiple obstetric and infectious disease guidelines address the health and management of the fetus and newborn exposed to varicella [72-74].

4.3.3 Herpes simplex virus

Several guidelines outline the management of genital herpes in pregnancy, which is outside the scope of this document [75-77]. While a small proportion (<2% estimated) of pregnant women will seroconvert to Herpes simplex virus (HSV), severe disseminated maternal infection is rare (there are < 40 cases reported in the literature [78, 79]). Features of disseminated HSV may include encephalitis, thrombocytopenia, leucopenia and coagulopathy [80]. Additionally, liver dysfunction has been a common presenting feature of these cases and HSV should be considered in the differential diagnosis of women with severe liver dysfunction in pregnancy [81]. A review of reported HSV hepatitis cases found 23% were in pregnant women, mortality was 88% if untreated and 51% in acyclovir treated patients [82]. Maternal mortality from herpes hepatitis from 2000 onward has been reported at approximately 9% [79].

4.4 Non-infectious conditions that can mimic sepsis.

In the pregnant or postpartum woman, a number of conditions may resemble aspects of the sepsis syndrome and should be considered in the differential diagnosis. These are listed in Table 4.2.

Table 4.2: 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

5. Investigations in sepsis

KEY POINTS

- ***Blood cultures and appropriate microbiological specimens should be obtained ideally prior to commencement; however this should NOT delay administration of antimicrobials.***
- ***Imaging should not be withheld just because the patient is pregnant or breast feeding***
- ***Reference pregnancy-appropriate normal ranges for investigations and observations***

GRADE EVIDENCE: HIGH QUALITY

Obstetric patients with infections may present with nonspecific symptoms and early investigation is necessary to exclude severe infection [64]. Maternity units should ensure observations are recorded on maternity specific charts on all obstetric and postpartum patients. Their utilization has been shown to promote earlier detection and therefore treatment of the women developing a critical illness [7].

Once infection is suspected, treatment should be commenced and the likely source and severity of sepsis elucidated via history, examination and further investigations. Investigations are directed at determining the etiology and risk stratification of sepsis as well as organisation of care for women in the most apropriate area. Sepsis during pregnancy will require matenal investigations as detailed below and fetal wellbeing assessment with cardiotocograph and /or ultrasound. Table 5.1 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. Table 5.2 lists additional investigations which can be undertaken depending on initial investigation results and the likely source of infection.

- Two sets of peripheral blood cultures should be taken sequentially immediately and 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 as determining

the etiology of the infection will allow for targeting of antimicrobial therapy. Other sites to consider are the urinary, genital and repiratory tract and surgical wounds including previous vascular access sites.

- Arterial blood gases should be undertaken to determine presence of hypoxia, hypercapnea, metabolic state and lactate level. If unable to obtain arterial lactate, level a venous level can be collected. Elevated lactate levels are an indication of tissue hypoperfusion with values greater than 2 mmol/L being associated with increased mortality in pregnancy[28]. The sampling site of the blood does not affect the lactate results (eg. arterial, venous or capillary [83]).

Table 5.1: First line investigations recommended for suspected sepsis

Investigation [33, 84-86]	Results in non-obstetric sepsis [33, 84-86]	Obstetric reference range (if relevant) [24]
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**	May be positive for organism	
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 MCS** **naso-pharyngeal aspirate/swab** **cerebrospinal fluid** **vaginal swabs** **stool culture**	May be positive for organism	
Arterial blood gases **–detect acidosis, hypoxaemia, lactate as below**		PaO_2 : 1st trimester: 93-100 mmHg 2nd trimester: 90-98mmHg 3rd trimester: 92-107mmHg $PaCO_2$: 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**	$\geq$ 2mmol/L associated with increased mortality	0.6-1.8 mmol/L
Full blood count	WCC >12 X10 9/L or <4 x10^9 /L Normal WCC count with > 10 % immature forms Thrombocytopenia is a severe sign of sepsis (Platelet count <100x10^9/L indicates organ dysfunction)	WCC 6-17 X 10^9 /L WCC in hours post-delivery between 9-15 X 10^9 (steroids also increase WCC) Platelets – lower limit of normal 150-420 x10^9/L

Coagulation studies	May be abnormal in sepsis with INR >1.5 , APTT > 60 secs and indicating organ dysfunction	No change
Creatinine urea and electrolytes - **Measure at baseline and until the patient improves** - **Elevated creatinine is a sign of severe sepsis** - **Abnormal electrolytes and elevated urea may be seen in sepsis**	Sepsis is severe if [87]: Creatinine >120µmol/L (presuming premorbid baseline renal function was normal)	Creatinine Varies with Gestation (reference ranges) : 1st trimester 35-62µmol/L 2nd trimester 35-71µmol/L 3rd trimester 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**	Plasma total bilirubin >70µmol/L indicates organ dysfunction	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	May show evidence of infection such as consolidation or pleural effusion	May show evidence of infection such as consolidation or pleural effusion. Diaphragm elevation may be distorted by fundus, cardiac axis rotated in pregnancy
Fetal Assessment – CTG and /or fetal ultrasound		A non-reassuring CTG suggests inadequate uteroplacental perfusion and may reflect maternal organ hypoperfusion

Table 5.2: Subsequent investigations to be considered in women with suspected sepsis

Investigation to Consider	Comments
Lumbar puncture	If meningitis or central nervous system infection is suspected
Echocardiogram	Useful in IV drug users or women with known cardiac anomalies to detect endocarditis. All women with blood cultures positive for staphylococcal bacteraemia should have an echocardiogram. May be useful in determining cardiac function
Imaging modalities - Pelvic ultrasound - Abdominal ultrasound - CT abdomen or chest	May define infective source or collection and allow drainage. Consider if localising symptoms or signs present or ongoing sepsis with unknown source
C reactive protein (CRP) Nonspecific investigation but can aid in monitoring treatment efficacy	Obstetric specific normal ranges[24]: CRP : 0.4-20.3mg/L
Viral Infections suggested from history, examination and other blood tests - Hepatitis A, EBV, CMV , HIV , Herpes , Varicella Zoster serology	
Clostridium Difficile - If patient has recently had antibiotics and develops diarrhoea	Send stool sample for microscopy, culture and sensitivity as well as for Clostridium difficile toxin
History of recent overseas travel	Consider testing for atypical infections and parasites. Trigger appropriate infection control mechanisms and consider CRE (Carbapenem-resistant Enterobacteriaceae)
Viral Infections suggested from history, examination and other blood tests - Hepatitis A, B, C, EBV, CMV , HIV , Herpes , Varicella Zoster serology	
Clostridium Difficile - If patient has recently had antibiotics and develops diarrhoea	Send stool sample for microscopy, culture and sensitivity as well as for Clostridium difficile toxin
History of recent overseas travel -consider testing for parasites	
Other atypical infections suggested from history e.g. Listeria monocytogenes- pregnant women are more susceptible.	Investigate with blood cultures (best for Listeria) and urine or stool cultures for other infections

Appropriate imaging should **not** be withheld because a woman is pregnant. Concerns about radiation exposure to her developing fetus or sensitive maternal breast tissue need to be balanced against the clinical need for imaging [88].

6. Treatment in the golden hour

KEY POINTS

- ***Commence resuscitation immediately to stabilize the mother.***
- ***Administer empiric therapy immediately and preferably within one hour***
- ***Commence thromboprophylaxis***
- ***Where a source of sepsis is localized, refine antibiotic prescribing to appropriate antibiotics***

GRADE EVIDENCE: MODERATE QUALITY

The treatment of women with suspected sepsis is multifaceted. Treatment should be commenced as soon as practical - ideally within the first hour ('golden hour') of sepsis being suspected. The treatment should include antimicrobials (antibiotics or antivirals as appropriate) as well as supportive therapies such as intravenous fluids and venous thromboembolism prophylaxis. Recommendations have been made on the currently available relevant obstetric literature where available.

6.1 Fluid resuscitation

In most circumstances the initial treatment of hypotension in sepsis is fluid administration. Fluid resuscitation is vital in sepsis to restore circulating volume and improve blood pressure and tissue perfusion. The preferred fluid for resuscitation is usually a crystalloid (usually 0.9% normal saline). The use of albumin (in an intensive care setting in a heterogeneous group of non-pregnant patients requiring intravascular fluid resuscitation) showed no overall improvement in mortality compared to normal saline for fluid resuscitation [89]. However, hydroxyethylstarch usage for resuscitation in patients with sepsis, conferred an increased mortality and need for renal replacement therapy compared to Ringer's acetate[90]. Blood may also be used as a means of fluid replacement if there is evidence of blood loss or severe anaemia. In the general ward setting, a maximum of 20mls/kg is appropriate to an absolute maximum of 2litres. Prior to further fluid administration, consider escalation to either intensive care or high dependency unit if the mean arterial pressure and other indices do not improve, where vasopressors may be required [91] (refer to 'Intensive Care Issues' below).

As part of the Surviving Sepsis Campaign [86] a number of 'care bundles' were introduced, focusing on <u>early</u> fluid resuscitation, prompt administration of antibiotics after appropriate cultures, targeting of physiological parameters such as a mean arterial pressure of >65mmHg and the monitoring of serum lactate levels [86]. These interventions focused on the first 6 hours of sepsis care, which typically would occur in an emergency department. This early goal-directed therapy (EGDT) has been re-evaluated in three subsequent harmonised international randomised controlled trials [92] [93], [94] including one primarily conducted in Australia and New Zealand [92]. None of these trials found any benefit of EGDT over usual care. It is worth noting that pregnant patients were excluded from these studies.

6.2 Thromboembolism prophylaxis

Both pregnancy and sepsis are independent risk factors for venous thromboembolism[95]. Thus prevention of deep venous thrombosis is critically important. Unfractionated heparin (UH) and low molecular weight heparin (LMWH) have been used extensively in pregnancy and been shown in large clinical trials to be effective in the prevention of thromboembolism [96]. LMWH has different pharmacokinetics to UH, however, they are both renally excreted and dose adjustment should be considered in women with renal dysfunction [97]. Consideration should be given to increasing the dose of thromboprophylaxis in obese women as there is data to suggest that weight based dosing is more likely to result in appropriate prophylactic anti-Xa levels[98]. Prophylactic dose LMWH should generally be ceased a minimum of 12 hours and UF heparin at least 6 hours prior to neuraxial analgesia or anaesthesia or surgery [11, 95, 99]. In certain settings such as intensive care, mechanical means of preventing thromboembolism are available and may be used.

6.3 Treatment in the 'Golden Hour' for bacterial sepsis

When a bacterial source of sepsis in pregnancy or postpartum is suspected, prompt treatment with antibiotics within one hour is important for maternal survival as mortality can increase by 8% for each hour's delay in administering antibiotics [100]. Following principles of antibiotic stewardship recommended in both Australia and New Zealand, selection of antibiotic treatment needs to be appropriate for the suspected infection, whilst minimizing the risk of adverse effects and reducing the emergence of antibiotic resistance[101, 102] .

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.

Where women are immunosuppressed by immunomodulators including biopharmaceuticals for solid organ transplant, malignancy or autoimmune disease; chronic infection including HIV; or significant medical co-morbidities such as diabetes, a physician should be involved in decision making as soon as possible after the diagnosis or recognition of sepsis. However, this should not delay antibiotic treatment.

6.3.1 Treatment of sepsis of unknown source

Table 6.1 outlines recommendations regarding empiric antibiotic treatment in the 'golden hour'. Considerations of antibiotic stewardship are pertinent here, and will be facilitated by obtaining advice from a physician experienced in treating sepsis in pregnancy. Traditionally, empiric antibiotic recommendations for pregnancy and postpartum have aimed to cover primarily obstetric sources of sepsis. These may still be appropriate in community acquired sepsis. However, as obstetric services are increasingly part of larger hospital networks, and the age of and number of co-morbidities of obstetric patients has increased, antibiotics administered in the golden hour will need to cover resistant isolates, non-reproductive tract sources of sepsis and also aim for simplicity and uniformity. Therefore, these guidelines have based empirical antibiotic recommendations for obstetric patients with sepsis of

unknown source, on national antibiotic guidelines for adults in general, whilst taking into account pharmacological considerations of pregnancy and lactation.

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 electronic Antibiotic therapeutic guidelines are available at the following URL: https://tgldcdp.tg.org.au/guideLine?guidelinePage=Antibiotic&frompage=etgcomplete

Table 6.1: Recommendations for antimicrobial treatment of sepsis with unknown source

	Australian [103] and New Zealand [103-105] Antibiotic Regimens	Alternative for penicillin hypersensitivity†:
Community-acquired sepsis (source not apparent)	Aus : **amoxicillin/ampicillin** 2g IV 6-hourly PLUS **gentamicin** 4-7mg/kg (first dose) IV* PLUS **metronidazole** 500mg IV 12-hourly NZ: **cefuroxime** 1.5g IV 8-hourly PLUS **gentamicin** 4-7mg/kg (first dose) IV * PLUS **metronidazole** 500mg IV 12-hourly If at risk of MSRA sepsis (based on previous swabs/cultures and local epidemiology): ADD **vancomycin** 25-30mg/kg (loading dose) IV * 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	Severe: **clindamycin** 600mg IV 8-hourly PLUS **gentamicin** 4-7mg/kg (first dose) IV* (NZ: seek expert advice due to increasing Group B strep resistance to clindamycin and macrolides [106]) Mild – moderate†: **cefazolin** 2g IV 6-hourly PLUS **gentamicin** 4-7mg/kg (first dose) IV* PLUS **metronidazole** 500mg IV 12-hourly
Hospital-acquired sepsis (source not apparent)	Aus: **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) NZ: **cefuroxime** 1.5g IV 8-hourly PLUS **gentamicin** 4-7mg/kg (first dose) IV * PLUS **metronidazole** 500mg IV 12-hourly At risk of MSRA sepsis¥ (based on previous swabs/cultures and local epidemiology or if line sepsis) ADD **vancomycin** 25-30mg/kg (loading dose) IV * At risk of multidrug-resistant Gram-negative organisms use as a SINGLE AGENT: **meropenem** 1g IV 8-houly 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	Severe: **ciprofloxacin** 400mg IV 8-hourly PLUS **vancomycin** 25-30mg/kg IV*

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

†Immediate hypersensitivity (anaphylaxis) or severe delayed hypersensitivity; drug induced liver injury or acute interstitial nephritis = severe. Mild/moderate = delayed hypersensitivity. * 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 [107]. ¥ MRSA risk: recent international travel to areas with a high prevalence of MDR organisms; prolonged hospitalization and previous colonization.

6.3.2 Treatment of sepsis of known source

Bacterial

Table 6.2 outlines antibiotic recommendation where a specific source of infection is identified. The final decision regarding duration of treatment should take into account the source and type of infection, clinical response and local microbiologist or infectious disease specialist advice.

Table 6.2 : Recommendations for antibiotic treatment for localised sources of sepsis

Clinical diagnosis	Australian [103] and New Zealand Antibiotic Regimens[104, 108, 109]	Alternative for penicillin hypersensitivity†
Female Genital Tract source antenatal and postnatal including: **Chorioamnionitis** **Endometritis (postpartum)** **Septic abortion** **Sepsis post miscarriage** **Puerperal sepsis**	Aus: **amoxicillin/ampicillin** 2g IV 6-hourly PLUS **gentamicin** 4-7mg/kg (first dose) IV * PLUS **metronidazole** 500mg IV 12-hourly NZ : as for Aus or **cefuroxime** 1.5g IV 8-hourly PLUS **metronidazole** 500mg IV 12-hourly	Severe: **gentamicin** 4-7mg/kg (first dose) IV* PLUS **azithromycin** 500mg IV daily PLUS **clindamycin** 600mg IV 8-hourly NZ seek expert advice due to increasing Group B strep resistance to clindamycin and macrolides[106] Mild – moderate†: **ceftriaxone** 2g IV daily OR **cefotaxime** 2g IV 8-hourly PLUS **azithromycin** 500mg IV daily PLUS **metronidazole** 500mg IV 12-hourly NZ: **cefazolin** 2 g initially, then 1 g 8-hourly PLUS **gentamicin** 4-7mg/kg (first dose) IV* PLUS **metronidazole** 500mg IV 12-hourly [105]

Urinary tract	Aus: **gentamicin** 4-7mg/kg (first dose) IV * PLUS **amoxicillin/ampicillin** 2g IV 6-houly (some NZ regions too, e.g. Waikato region)[108] NZ: **cefuroxime** 750mg-1.5g IV 8-hourly OR **gentamicin** 4-7mg/kg (first dose) IV * alone <u>If gentamicin use is contraindicated, use as a SINGLE AGENT:</u> **ceftriaxone** 1g IV daily OR **cefotaxime** 1g IV 8-hourly <u>If anti-pseudomonal cover is required,</u> use as a SINGLE AGENT: **ceftazidime** 1g IV 8-hourly OR **gentamicin** 4-7mg/kg (first dose) IV * OR (if Extended spectrum beta-lactamase producers suspected): **meropenem** 1g IV 8-hourly	Severe: **gentamicin** 4-7mg/kg (first dose) IV * alone Mild – moderate[†]: cephalosporin e.g. **cefuroxime** 750mg-1.5g IV 8-hourly OR **ceftriaxone** 1g IV daily
Wound infection	Post C-section: **flucloxacillin** 2g IV 6-hourly (4-hourly for severe sepsis requiring ICU, septic shock) Post episiotomy ADD **gentamicin** 4-7mg/kg (first dose) IV * New Zealand:ADD **metronidazole** 500mg IV 12-hourly Infected post-op abdominal wounds: as for peritonitis MRSA suspected: ADD **vancomycin** 25-30mg/kg (loading dose) IV * to **flucloxacillin** or **cefazolin**	Severe: **vancomycin** 25-30mg/kg (loading dose) IV * Mild – moderate: **cefazolin** 2g IV 8-hourly
Mastitis – postpartum/lactating	**Flucloxacillin** 2 g IV 4- to 6-hourly (4-hourly for severe sepsis requiring ICU, septic shock) assumes methicillin sensitivity (MSSA) If MRSA carrier, use: **vancomycin** 25-30mg/kg (loading dose) IV *	Severe: **clindamycin** 600mg IV 8-hourly Mild – moderate: **cefazolin** 2 g IV 6- to 8-hourly
Bacterial pneumonia	Australia: **ceftriaxone** 1g IV daily OR **cefotaxime** 1g IV 8-hourly PLUS **azithromycin** 500mg IV daily x 3-5 days (Tropical regions of Australia: refer to Therapeutic Guidelines[103]) New Zealand: **cefuroxime** 1.5g IV 8-hourly PLUS macrolide (**azithromycin** 500mg IV daily or **erythromycin** 1g IV 6-hourly)	Severe: **moxifloxacin** 400mg PO/IV daily) PLUS **azithromycin** 500mg PO daily x 3-5 days

Acute abdomen with suspected perforation OR post-operative abdominal sepsis	**amoxicillin/ampicillin** 2g IV 6-hourly PLUS **gentamicin** 4-7mg/kg (first dose) IV* PLUS **metronidazole** 500mg IV 12-hourly	Severe: **clindamycin** 600mg IV 8-hourly PLUS **gentamicin** 4-7mg/kg (first dose) IV* Mild – moderate: **cefazolin** 2g IV 6-hourly PLUS **gentamicin** 4-7mg/kg (first dose) IV* PLUS **metronidazole** 500mg IV 12-hourly
Epidural/Spinal abscess	**gentamicin** 4-7mg/kg (first dose) IV* PLUS **flucloxacillin** 2g IV 4 to 6-hourly	Severe: **gentamicin** 4-7mg/kg (first dose) IV* PLUS **vancomycin** 25-30mg/kg (loading dose) IV * Mild – moderate or gentamicin contraindicated: **ceftriaxone** 4 g IV daily OR **ceftriaxone** 2g IV 12-hourly OR **cefotaxime** 2g IV 6-hourly
Bacterial Meningitis (cover N. meningitides, H. influenzae and Listeria)	**ceftriaxone** 4 g IV daily or 2 g IV 12-hourly PLUS **benzylpenicillin** 2.4g IV 4-hourly or **amoxicillin** 2g IV 4-hourly (for listeria cover) PLUS dexamethasone 10mg IV 6-hourly for 4 days If CSF typical for bacterial meningitis ADD **vancomycin 25-30mg/kg** IV (to cover *streptococcus pneumoniae*)	Any hypersensitivity to penicillins: **vancomycin*** IV PLUS **ciprofloxacin*** 400mg IV 8-houly Or **moxifloxacin*** 400mg IV daily
Listeriosis	**benzyl penicillin** 1.2g IV 6-houly or **amoxicillin/ampicillin** 2g IV 6-hourly +/- **gentamicin** 4-7mg/kg (first dose) IV*	Hypersensitivity to penicillins**: trimethoprim+ sulfamethoxazole** 5mg/kg IV 6-hourly

*** 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[107]**

† Immediate hypersensitivity (anaphylaxis) or severe delayed hypersensitivity.

6.3.3 Treatment of sepsis of viral etiology

6.3.3 Viral infections

Influenza

Neuraminidase inhibitors (oseltamivir, zanamivir)

Neuraminidase inhibitors are recommended for the treatment of influenza [110]. Neuraminidase has a role in the promotion of release of viruses from infected cells, and the inhibition of neuraminidase results in aggregation of the viral particles at the host cell surface, and a reduction in the amount of virus released to infect other cells.

Oseltamivir (Tamiflu) has more obstetric safety data available than zanamivir (Relenza) and is the agent of choice in pregnancy [111]. There is a low rate of transplacental transfer, estimated at between 1-14% of maternal concentrations in ex vivo perfusion studies [112]. In the setting of H1N1 pandemic influenza in pregnancy, early antiviral therapy (initiation < 2 days) was associated with an 84% reduction in admissions to intensive care [113]. Further, only 7% of pregnant women who died from H1N1 received treatment with a neuraminidase inhibitor within two days compared with 41% of those who survived [114]. Advice for prevention and treatment is listed in Table 6.3. A recent pharmacokinetic study demonstrated that levels are 30% lower in the pregnant compared with non-pregnant adult. Therefore in severe illness consider using higher doses[115].

Table 6.3: Prevention and treatment of influenza.

Post-exposure prophylaxis and treatment	• Oseltamivir (Tamiflu™) • Prophylactic dose: 75mg orally, taken daily for 7-10 days after exposure. • Treatment dose: 75mg capsule orally twice daily for 5 days. In a woman with symptoms consistent with influenza infection, oseltamivir should be started as soon as possible, preferably within 48 hours.

Influenza vaccine:

The World Health Organisation and the Global Influenza Initiative recommend women are vaccinated for influenza at any stage during pregnancy using the inactivated influenza vaccine [105, 116]. The inactivated vaccine is safe in pregnancy [116]. While injection site reactions have occurred no other evidence of increased risk of maternal or fetal adverse outcomes from the inactivated influenza vaccine have been reported to date [116]. In Australian data, a prospective cohort study of 1086 pregnant women and 314 non pregnant female health care workers given the trivalent influenza vaccine in 2014 reported no serious vaccine related adverse events, and no increase in reporting of adverse events in the pregnant women compared to the non-pregnant women [117].

Pregnant women have a similar immune response to the inactivated influenza vaccine as non-pregnant women [118]. Vaccination rates in Australia remain poor, but are improving,

with a recent study showing maternal uptake of the influenza vaccine rising from 29.6% in 2010, to 51.3% in 2014 [119, 120].

The inactivated influenza vaccine has been shown in randomised trials to reduce the rates of maternal febrile respiratory illness by approximately 35%, laboratory confirmed influenza by 50% and in large registry studies the monovalent H1N1 vaccine or seasonal influenza vaccine reduced clinical diagnoses of influenza by 44-70% [121]. Administration of the inactivated influenza vaccine during pregnancy also confers protection to the infant, reducing laboratory confirmed influenza by up to 60% with a 40-45% reduction in hospitalizations [121].

Varicella

Zoster Immunoglobulin should be offered to sero-negative women with significant exposures to either acute varicella or herpes zoster (shingles) within 96 hours of exposure [70, 122, 123]. A significant exposure is considered to be: living in the same household as a person with chickenpox or zoster, face to face contact for at least 5 mins or in the same room for at least one hour [72]. In pregnant women with significant exposure who present beyond 96 hours, post-exposure prophylaxis with oral acyclovir should be considered in sero-negative women at high risk of developing severe lung disease (eg immunosuppressed women.

Pregnant women with symptoms or signs of pneumonia require appropriate investigation and hospitalisation. Intravenous acyclovir has been recommended for treatment of women with respiratory complications [70, 123] . Use of acyclovir during pregnancy is outside the drug license, however, no adverse effects on a fetus or newborn have been attributed to acyclovir [124]. The pharmacokinetics of acyclovir are not altered by pregnancy [125, 126]. Acyclovir crosses the placenta, with the cord to maternal plasma concentration estimated at 1.3 [112]. While based on case reports and case series, maternal and fetal mortality are reduced by the use of acyclovir in the setting of varicella pneumonia [127].

Herpes simplex virus

Intravenous acyclovir is first line therapy for disseminated disease. Foscarnet has been used in drug resistant infection outside pregnancy. There are only two case reports of Foscarent use in pregnancy in the setting of severe genital HSV with HIV co-infection, and with a normal newborn examination [128] and fulminant herpes hepatitis [79].

6.4 Potential maternal adverse effects of antibiotics

As with all patients administered antibiotics, there are potential adverse reactions that may occur. These can include allergic reactions, diarrhoea, idiosyncratic drug-induced renal or liver injury.

Allergic or hypersensitivity reactions can occur in several circumstances. These include:

(i) IgE mediated immediate reactions (i.e. anaphylaxis) which may be life-threatening or

(ii) delayed (non-immediate) reactions. The delayed reactions can occur in a variety of forms: mild to moderate (usually rash) or severe (e.g. Stevens-Johnsons syndrome)[103].

Diarrhoea may also occur in which case a stool sample for C. difficile toxin testing should be requested. The mortality of C. difficile colitis is up to 30% in mothers if untreated[129]

Renal impairment and ototoxicity can occur specifically with the use of vancomycin and aminoglycosides (e.g. gentamycin) particularly at supra-therapeutic levels or when these antibiotics are used for extended periods of time. Their therapeutic dosing and monitoring should follow local guidelines.

Idiosyncratic drug-induced renal injury can occur in the form of acute interstitial nephritis (AIN) or tubule-interstitial nephritis (TIN). This is a differential diagnosis for acute kidney injury (AKI) in the setting of treated sepsis, particularly with beta lactam antibiotics. A renal biopsy may sometimes be required for a definitive diagnosis to be made. AIN usually responds to cessation of the offending drug (although this can take some time for recovery to be observed) and recurs with re-exposure[130]. Treatment with corticosteroids may be required.

Idiosyncratic drug induced liver injury (DILI) may be either hepatocellular or cholestatic in nature. This injury is associated with many drugs, especially antibiotics including penicillins and cephalosporins. The reaction is often delayed days to weeks from antibiotic administration, late abnormalities of liver function will need to be investigated to exclude other pregnancy related causes of liver dysfunction. If these are normal, a late drug reaction may be assumed. It is important to diagnose drug-related liver dysfunction to prevent re-administration and further liver damage at another time in the future [131].

6.5 Pharmacological considerations for pregnancy and breastfeeding

Concerns regarding pregnant and breastfeeding women being exposed to antibiotics may be raised. In the case of appropriate sepsis treatment, the risk of maternal and fetal morbidity and mortality is higher than the benefit of non-exposure. Antibiotic therapy should be de-escalated as soon as possible in the interest of maintaining a normal gut microbiota in the infant as well as the mother. Maternal intrapartum antibiotic exposure has been shown to impact the gut microbiota of infants. Disrupted microbiota may be associated with obesity and immune dysfunction later in life. Breast feeding helps reverse this disruption[132]. Studies[133] are investigating the role of probiotics in pregnancy, although to date there is no conclusive evidence supporting their use.

While most antibiotics are found in breastmilk of a lactating woman, the relative infant dose is generally small. However, 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 breastfeeding mothers. (URL:https://tgldcdp.tg.org.au.acs.hcn.com.au/quicklinks?type=Pregnancyandbreastfeeding).

6.6 Infection prevention and control considerations

Infection control measures including contact precautions should be considered and discussed with local infection control colleagues. Women suspected of, or diagnosed with an infectious disease, should be isolated in a single room with en-suite facilities for 24 hours after effective antibiotic treatment has been commenced. Unwell visitors should be instructed to refrain from visiting maternity areas to avoid transmission to pregnant and postpartum women[134].

Some infections are notifiable to the local health department [135], in particular Group A Streptococcus (GAS) [136]. GAS in close contacts and family members is a risk factor for maternal, particularly postpartum sepsis. HCWs who have been exposed to respiratory secretions of women with GAS infection should be considered for antibiotic prophylaxis.

7. Fetal surveillance

KEY POINTS

- ***Consider the most appropriate method of monitoring fetal wellbeing during maternal sepsis. eg cardiotocography, ultrasound, Doppler auscultation***
- ***If preterm delivery is required, corticosteroids should be considered for fetal indications***
- ***Chorioamnionitis onset may be non-specific or insidious, but rapid deterioration is possible. Chorioamnionitis requires urgent delivery on both maternal and fetal grounds***
- ***Preterm delivery may be required for fetal or maternal indications***
- ***Perimortem caesarean section (resuscitative hysterotomy) should be considered in cases of maternal cardiorespiratory arrest beyond 20 weeks gestation.***

GRADE EVIDENCE: MODERATE QUALITY

In the setting of sepsis, the goal of fetal surveillance is to assess fetal well-being as well as to determine the presence of intrauterine and fetal infection. Non-invasive fetal surveillance relies on the modalities of electronic fetal monitoring (EFM) [137] and ultrasound, while invasive techniques such as amniocentesis may play a role in assessing the presence of intrauterine infection and establishing a microbiological diagnosis.

The decision to undertake fetal surveillance and the mode of fetal surveillance during maternal sepsis will be determined by fetal gestation and the facilities available in the healthcare unit. For example, fetal surveillance at pre-viable gestations (i.e. prior to 24 weeks) may be limited to ultrasound assessment of fetal viability, whereas assessment at later gestations beyond 26 weeks may include EFM.

In the setting of extra-uterine sepsis (eg respiratory or urinary sepsis), fetal well-being will largely be determined by maternal status. EFM may demonstrate an uncomplicated fetal tachycardia characterised by acceptable short term variability and absence of decelerations.

These findings will often improve with maternal fluid resuscitation and treatment of maternal pyrexia and may increase the possibility of a relatively reassuring fetal heart rate pattern despite acute maternal sepsis[138].

In contrast, there is a lack of sensitivity and specificity in the EFM findings observed in cases of intrauterine sepsis [139, 140]. Nevertheless, features suggestive of fetal acidosis including reduced or absent variability, baseline tachycardia and/or the presence of persistent late decelerations warrant further assessment and expedited delivery [137], taking into account the maternal status and ensuring that appropriate maternal resuscitation has been undertaken to allow a safe birth [138].

The role of ultrasound in assessing fetal wellbeing has been investigated predominantly in the setting of women with preterm premature rupture of membranes (PPROM) and as a means of detecting the development of intra-amniotic sepsis. Two studies have investigated the role of the biophysical profile in assessing fetal well-being and despite some methodological limitations of these studies; both concluded biophysical profiles are not useful in predicting the development of intra-amniotic infection [141, 142].

7.1 Timing and mode of delivery

The timing of delivery will be determined by:

- The presence of intrauterine sepsis
- The nature of the maternal sepsis and response to initial resuscitation efforts
- The gestation of the pregnancy and fetal status

In the setting of intrauterine sepsis, delivery should always be considered regardless of the gestation. At pre-viable gestations (less than 23 weeks), where there is little chance of fetal survival, induction of labour is in the maternal interest and reduces the risk of surgical infection compared to operative delivery. At more advanced gestations, the decision regarding mode of delivery must be weighed up carefully, taking factors such as the cervical favourability and hence likelihood of a quick birth, the fetal presentation and chance of neonatal survival, the maternal condition and the suitability of the environment (eg Intensive care unit vs birthing suite) into consideration. Commonly, an emergency caesarean section will be required as a means of expediting delivery. Where delivery of a preterm infant is anticipated, this should be undertaken in a facility with access to an appropriate level nursery and neonatal support.

Corticosteroids should be considered for fetal lung maturation but this decision needs to be balanced against the urgency of delivery [143]. While the majority of randomised trials investigating the role of corticosteroids in improving neonatal respiratory outcomes excluded women with chorioamnionitis, four trials[144-147]included a proportion of women with chorioamnionitis. In trials that excluded women with chorioamnionitis no significant increase in the rates of puerperal sepsis were reported[143]. The neonatal benefits (decreased respiratory distress and perinatal death) of antenatal corticosteroids for infants born to women with chorioamnionitis are similar to the benefits achieved when corticosteroids are given to women without chorioamnionitis [143]. Unfortunately only 2 of these trials reported the rates of puerperal sepsis[146, 147]. Evaluation of the studies that included women with

chorioamnionitis suggested a 2.65 fold increase (95% confidence interval 1.18-5.91) in the rates of puerperal sepsis in women who received antenatal corticosteroids [138]. These findings should be interpreted with caution given the limited data and wide confidence intervals. Nevertheless, it is imperative that corticosteroids are considered when maternal status allows, but delivery should not be delayed in women with chorioamnionitis simply to administer corticosteroids. Women with chorioamnionitis who receive antenatal corticosteroids should be observed closely due to the possible increased risk of developing puerperal sepsis [143].

There is accumulating evidence of the increasing risks of cerebral palsy in association with exposure to intrauterine sepsis, thereby highlighting the need to expedite delivery in fetuses at more advanced gestations with proven or high likelihood of intrauterine sepsis [148, 149]. A recent meta-analysis identified 12 studies that investigated the association between clinical chorioamnionitis and cerebral palsy and reported a pooled odds ratio of 2.42 (95% confidence interval 1.52-3.84) [150]. However, the studies included in this meta-analysis have a range of limitations including the use of a "clinical diagnosis" of chorioamnionitis, the variable use of microbiological techniques for detection of causative pathogens and the heterogeneity of the included studies.

Intrauterine sepsis should be suspected in the presence of maternal fever, (although fever is not essential) and the presence of associated risk factors such as ruptured membranes or recent intrauterine procedures such as amniocentesis[151]. Additional clinical signs include maternal tachycardia, fetal tachycardia, uterine tenderness, offensive vaginal discharge and maternal leucocytosis. It is important to remember that while the onset of chorioamnionitis may be non-specific and insidious, rapid deterioration is possible. Likewise, it is relevant to note fever may not be a feature in a woman who is developing sepsis and deteriorating rapidly.

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. Alterations in maternal physiology in late pregnancy such as the effects of the gravid uterus on the inferior vena cava, (causing supine hypotension) and diaphragm (reduced vital capacity), increased cardiac output and altered capillary permeability, can all contribute to increasing the difficulties associated with resuscitation.

Assessing the response to maternal resuscitation and treatment is a vital component of the assessment and management of sepsis in pregnancy. Delivery should be considered in any case where the maternal response to treatment is felt to be compromised by the pregnancy. For example, women with significant respiratory sepsis or acute respiratory distress syndrome (ARDS) may be difficult to ventilate adequately due to the raised intra-abdominal pressure caused by pregnancy at more advanced gestations [138]. The question regarding whether delivery may improve or further compromise resuscitation efforts should always be considered carefully with decisions made by an experienced multidisciplinary team [138]. In one of the largest studies to date regarding the indications for delivery in women with extra-uterine sepsis, the presence of septic shock, multi-organ failure or worsening respiratory status were regarded as the leading indications for delivery [152].

7.2 Premature labour in cases of sepsis

Urinary tract sepsis such as pyelonephritis may in fact trigger labour. While efforts to suppress premature labour by using tocolytic agents (such as nifedipine) in the setting of extra-uterine sepsis should be considered, careful attention to exclude intrauterine sepsis if possible should be taken due to the risks of cerebral palsy described previously. Where labour is suppressed, this should be limited to a defined short period to allow corticosteroids to be administered for fetal lung maturation and transfer if required to an appropriate tertiary facility. Close fetal and maternal surveillance should be undertaken to exclude any evidence of fetal compromise where labour is suppressed.

7.3 Peri-mortem caesarean section

In the event of maternal cardiorespiratory arrest in cases of severe maternal sepsis, peri-mortem caesarean section should be considered. Multiple case reports and case series have demonstrated an improvement in the ability to resuscitate women following cardiorespiratory arrest due to relief of aorto-caval compression as well as reducing the metabolic requirements [153, 154]. While traditionally regarded as being in the maternal interest, these series have demonstrated improved neonatal survival with early recourse to caesarean section [154]. Even at extreme preterm gestations where neonatal survival is considered to be unlikely, peri-mortem caesarean section is recommended to improve the chances of successful maternal resuscitation, hence the recommendation that it be renamed resuscitative hysterotomy and be performed in the event of maternal arrest if the uterus is palpable at or above the umbilicus (equivalent to 20 weeks gestation), regardless of the presence or absence of fetal cardiac activity. [155]. Furthermore, previous recommendations that surgery should commence within 4 minutes of arrest with the aim of achieving delivery within 5 minutes have now been abandoned in favour of a recommendation that surgery commence immediately coinciding with maternal resuscitation efforts, since analysis of case reports and series demonstrates both improved maternal and neonatal outcomes with shorter intervals between commencement of resuscitation and delivery. [156]

8. Role of the anesthetist in managing maternal sepsis

KEY POINTS

- ***Neuraxial blocks in women with untreated sepsis may be undertaken only after careful consideration due to increased risk of complications in the short and long term.***
- ***Pregnant women with sepsis experience increased haemodynamic instability during general anesthesia***
- ***Anesthesia during pregnancy in a woman with sepsis does not increase mortality but may be associated with other adverse obstetric events.***

GRADE EVIDENCE: LOW QUALITY

The role of the anesthetist in managing maternal sepsis includes:

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

8.1 Initial care and stabilisation

The anesthetist is often called upon, as a member of the multidisciplinary team and in particular to assist with vascular access, invasive monitoring, initial management and stabilisation of the parturient with sepsis. The principles of managing obstetric patients with sepsis are the same as those for non-pregnant patients.

8.2 Patient transfer

The management of women with sepsis may involve diagnostic imaging, interventional radiology, surgical procedures, and complex treatment such as positive pressure ventilation, inotropic therapy, extra corporeal membrane oxygenation and haemo-filtration in a tertiary intensive care unit. Elements of care will include: safe transport of a compromised patient with reduced physiological reserve; accurate patient assessment and optimisation; co-ordination and effective communication between members of the multi-disciplinary team and utilisation of trained personnel supported by skilled assistance and appropriate equipment. Furthermore, the transport team must be experienced in securing airways, ventilation, resuscitation and other anticipated emergency procedures. In addition, a comprehensive hand over should take place at the receiving facility. The responsibility of intra and inter-hospital transfers often rests with the anaesthetist to provide the standard of care as set out in The Australian and New Zealand College of Anaesthetists 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” [157].

8.3 Intra-operative care

The obstetric patient with sepsis may require anaesthesia for delivery of her fetus or infection control procedures such as removal of the septic focus including drainage of an abscess and debridement of necrotic tissues. The intra-operative management goal is to provide optimal care to a patient with deranged physiology and altered drug handling secondary to the systemic inflammatory response superimposed on pregnancy. For the mother, the aim is to maintain physiological homeostasis: preventing hypotension, hypoxia and hypercapnia, and for the fetus the focus is on optimisation of utero-placental perfusion to avoid fetal asphyxia, minimising unnecessary drug exposure, and the avoidance of preterm labour and fetal loss.

8.4 Delivery

The timing of delivery ultimately rests with the obstetrician, however, co-ordination with resuscitative measures needs to be taken into consideration. Even though neuraxial

blockade has generally been the anaesthesia of choice for operative delivery, there are a number of issues for the parturient with sepsis.

8.4.1 Spinal anaesthesia

Firstly, 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 blocks [158]. However, epidural anaesthesia carries a greater risk of infectious complications than spinal techniques [159].

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 basis [86, 160, 161]:

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.

Furthermore, the development of coagulopathy and hemodynamic instability are added contraindications to neuraxial blockade in the septic patient. In the case of hemodynamic instability, hypotension secondary to sympathectomy will be poorly tolerated.

8.4.2 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 empting with increased risk of reflux and aspiration.

Recommendations:

- Premedicate with combination antacid antihistamine prophylaxis, e.g. effervescent ranitidine 150mg
- rapid sequence induction

B - Breathing

Increased metabolic demand leading to accelerated hypoxaemia during periods of apnoea.

Recommendations:

- adequate pre-oxygenation prior to anaesthesia induction

Reduced functional residual capacity with increased ventilation/perfusion mismatch.

Recommendations:

- ventilation strategies to maintain oxygenation and minimise further lung injury

C - Circulation

Maintenance of systemic blood pressure for adequate organ perfusion, including placental bed.

Recommendations:

- avoidance of aortocaval compression using a lateral uterine tilt
- adequate fluid resuscitation including the appropriate use of blood products
- inotropic support – alpha adrenergic agonists (specifically noradrenaline) being agents of choice for maintenance of uteroplacental flow

8.5 Anaesthetic agent

No particular anaesthetic agent or technique has been recommended for the septic patient. Commonly used intravenous and inhalation agents all cause hypotension from vasodilatation and /or myocardial depression. It is not the agent, rather the care with administration, judicious dose in a titrated manner; that ensures a smooth induction of anaesthesia.

When surgical procedures for sepsis control are necessary, the pregnant woman should be reassured that to date, no anaesthetic agent has been shown to be clearly harmful to the human fetus. When used in clinically relevant doses/concentrations, there is no proof of teratogenicity in humans with the following [162, 163]:

- volatile agents
- barbiturates, ketamine, benzodiazepines
- opioids
- local anaesthetics
- muscle relaxants (these polarized molecules do not cross the placenta in significant amount)

Furthermore, it is uncertain whether results from animal studies suggesting anaesthetic agents influence early brain development by alteration of anatomical organization and functional consequences in the form of learning and memory deficit, can be extrapolated to the human fetal brain [164].

8.6 Non-obstetric surgery in the pregnant patient with sepsis

While modern surgical and anaesthesia techniques have rendered non-obstetric surgery safe for the pregnant woman [165, 166], they carry a risk for adverse fetal outcomes (premature labour, prematurity and fetal loss) which may be related to the underlying disease process rather than the warranted treatment. Moore *et al*[166] demonstrated no significant difference in overall mortality or 30 day mortality rates in pregnant and non-pregnant matched women undergoing similar surgical operations. Cohen-Kerem[165] *et al* reviewed pregnancy outcomes following non-obstetric surgery and their findings are summarised in Table 8.1.

Table 8.1: Pregnancy outcomes following non - obstetric surgery.

Event	Incidence
Maternal death	0.06%
Miscarriage	5.8% - all trimesters 10.5% - 1st trimester
Premature labour	3.5%
Fetal loss	2.5%
Prematurity	8.2%
Major birth defects associated with non-obstetric surgery in 1st trimester	3.9% (1 -3% in general population)

9. Intensive Care Issues

KEY POINTS

- ***Liaise with intensive care if the patient has cardiorespiratory compromise, evidence of end organ dysfunction or hypoperfusion***
- ***There is a paucity of data regarding the resuscitation of pregnant women in the intensive care unit. The preferred fluid is an isotonic crystalloid.***
- ***Admit to ICU when despite adequate fluid resuscitation there is ongoing hypotension with evidence of systemic hypoperfusion (eg an elevated lactate).***
- ***Tachypnea and/or hypoxia should prompt an urgent diagnostic evaluation and intensive care opinion.***

GRADE EVIDENCE: LOW QUALITY

Fortunately, the need for maternal intensive care unit (ICU) admission is uncommon. The most common reasons for ICU admission in this patient population are the hypertensive disorders of pregnancy and obstetric haemorrhage [167]. Sepsis is also amongst the leading causes of maternal ICU admission [168].

Intensive care is a largely centralised resource and is often not immediately available in many healthcare settings caring for pregnant women. The relative lack of need for ICU admission in these women may lead to uncertainty about referral criteria and recognition of the need for treatment escalation by maternity staff. Equally, many ICU staff (both medical and nursing) may be unfamiliar with obstetric patients and their particular diagnostic and management issues, leading to higher levels of uncertainty and anxiety about both the need for admission and subsequent management choices.

9.1 The deteriorating patient

Patients with sepsis may deteriorate rapidly and catastrophically. For hospitalised patients, the introduction of rapid response teams to intervene early in deterioration has been associated with a reduction in hospital mortality and cardiopulmonary arrest [169]. However, even if recognition of deterioration occurs, activation of the rapid response team may not

occur in up to 40% of instances [170]. In the obstetric setting there is minimal evidence concerning generic rapid response teams, and the need, (if any), for modification of the calling criteria or team composition. Specific obstetric early warning scores have been developed [171] and this guideline strongly recommends their use.

9.2 Triaging patients that require admission to the ICU

There is currently no well validated or absolute predictive scoring system that can reliably predict which of these patients will need ICU admission. The decision to admit to the ICU should be taken in consultation with the intensive care and the multidisciplinary obstetric teams. It should be recognised that the threshold for ICU admission may vary across settings, for reasons of skill mix and familiarity described above. Inter hospital transfer to a setting with greater capability or experience with these women may be necessary.

The Royal College of Obstetricians Greentop Guideline on Bacterial Sepsis [84] lists indications for transfer to ICU. Most of these indications comprise either signs of worsening organ dysfunction or increasing clinical instability (refractory hypotension despite fluid resuscitation, worsening acidosis, renal failure etc). Ideally, intensive care input should predate the development of many of these conditions.

9.3 Indications for intensive care involvement

Adequate initial resuscitation and treatment may result in stabilisation and prevent progression and deterioration, averting the requirement for intensive care. However, as stated above it is preferable that an ICU opinion and /or admission occur before the development of severe complications such as frank organ failure or catastrophic shock. If clinical concern exists then escalation of care should be considered early. Table 9.1 sets out in general terms when an ICU opinion should be obtained and ICU admission considered.

Depending on the woman's normal blood pressure, hypotension may be difficult to define but a reasonable starting point would be a systolic blood pressure of <90mmHg (mean arterial pressure <60-65mmHg): this cut-off may be higher if other signs of hypoperfusion exist.

Table 9.1: 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	

9.3.1 Tachypnoea and hypoxia

There is evidence from the non-obstetric population that tachypnoea and a need for high concentrations of supplemental oxygen are the early warning criteria most strongly associated with life threatening adverse events [172]. Although the normal physiological changes of pregnancy result in a respiratory alkalosis, this does not result in an increased respiratory rate. It should always be remembered that aside from cardiorespiratory or thromboembolic causes tachypnoea may be the result of sepsis or a resultant or co-existent metabolic acidosis. Evaluation of a venous or arterial blood gas will help to discriminate causes as well as providing very important metabolic information. Hypoxia is a most worrying sign, and warrants urgent consideration of escalation of care and a full diagnostic workup. The potential for severe maternal and fetal compromise with worsening hypoxia, plus potentially difficult maternal airway management, mandates early recognition and action.

9.4 Intensive care management

Although mostly beyond the scope of this document, the management of obstetric sepsis in the ICU is similar to that of the non-obstetric patient. There is an extremely limited evidence base regarding intensive care management of obstetric patients in general, and no specific evidence available for the patient with sepsis.

Similarly to the non-obstetric patient, ICU management in the obstetric population involves maintenance of physiological parameters and organ supports (supportive care) with directed care as and when possible (targeted antibiotic therapy, source control etc). Both invasive (e.g. intra-arterial access, central venous access) and non-invasive modalities such as echocardiography are used for close monitoring and to obtain detailed physiological data. Other invasive monitoring e.g. pulmonary artery catheterisation, intracranial pressure monitoring are used on a case by case basis. The normal physiological changes of pregnancy should be kept in mind when interpreting the data obtained.

In addition to the sepsis management and resuscitation described above, ongoing management principles include optimisation of volume status, maintenance of cardiac output, blood pressure and tissue perfusion, maintenance of metabolic homeostasis (including acid base and glucose status) and the provision of adequate oxygenation and ventilation. Every effort should be made to preserve tissue oxygenation and placental perfusion. The various organ supports employed will depend on the organ systems affected and the nature of the site/presentation/manifestation of sepsis and its subsequent complications.

Adjunct therapies for sepsis in intensive care have usually excluded the pregnant population from clinical trials, and have had in general limited success. More general management areas include deep venous thrombosis (DVT) prophylaxis, adequate analgesia, skin protection and care, stress ulcer prophylaxis, bowel care and the provision of adequate nutrition (oral, enteral or parenteral, being mindful of the increased demands of pregnancy). In the case of the still pregnant patient, certain extra principles should be observed, see Table 9.2 below.

Table 9.2: Unique considerations when caring for pregnant ICU patients

Considerations/practice points when caring for the pregnant ICU patient
• **Fetal wellbeing should be considered when setting physiological targets and monitoring should be undertaken by the obstetric team. There is minimal evidence available to guide practice.**
• **Care with medication prescribing**
• **Avoidance of unnecessary radiological procedures, and care with radiation exposure when radiology is necessary**
• **Avoidance of supine positioning with maintenance of lateral tilt at all times.**
• **Delivery may be required for maternal or fetal indications.**

In the case of the immediately postpartum woman, perineal care, breast care and lactation issues should be carefully monitored, especially in the unconscious patient. It is important to facilitate contact between mother and newborn when appropriate to do so.

10. Recommendations for research or audit

There is paucity of evidence specifically assessing the investigation, management or outcomes of pregnant women with sepsis. Below we have suggested a summary of suggested areas for future research. These investigations could be undertaken at a local level as a means of auditing the implementation of the SOMANZ sepsis guidelines.

Assessment of Sepsis

- What is the incidence of sepsis as a proportion of all births?
- What proportion of patients diagnosed with sepsis where screened using omqSOFA?

Fever in Pregnancy

- What proportion of pregnant women presenting with fever were administered anti-pyretics?

Etiology of Sepsis

- What is the prevalence of the different microorganisms causing sepsis?
- What proportion of all infections are caused by GAS?

Investigations in Sepsis

- What proportion of women with sepsis had blood cultures taken?

Treatment in the Golden Hour

- What proportion of women were administered intravenous fluids within the first hour of the suspicion of sepsis?
- What proportion of women with sepsis were administered empiric antibiotics within the first hour?

Fetal Surveillance

- What proportion of fetuses of a suitable gestation (greater than 24 weeks) were assessed with electronic fetal monitoring whilst treating the woman with sepsis?

Role of the Anesthetist in Managing Maternal Sepsis

- What proportion of pregnant women with sepsis undergo anesthetic consultation?
- What proportion of pregnant women with sepsis, having received neuraxial blockade develop complications, in particular haemodynamic and neurological?

Intensive Care Issues

- What proportion of women with sepsis required intensive care admission?
- What proportion of women with sepsis who had evidence of end-organ dysfunction were referred to intensive care?

Appendix 1

The complete SOFA (Sequential (sepsis related) Organ Failure Assessment) score is detailed in Table A.1. The SOFA score allows a score to be calculated based on the severity of various biochemical result, clinical signs and clinical interventions.

Table A1.1 : Sequential (sepsis related) Organ Failure Assessment Score

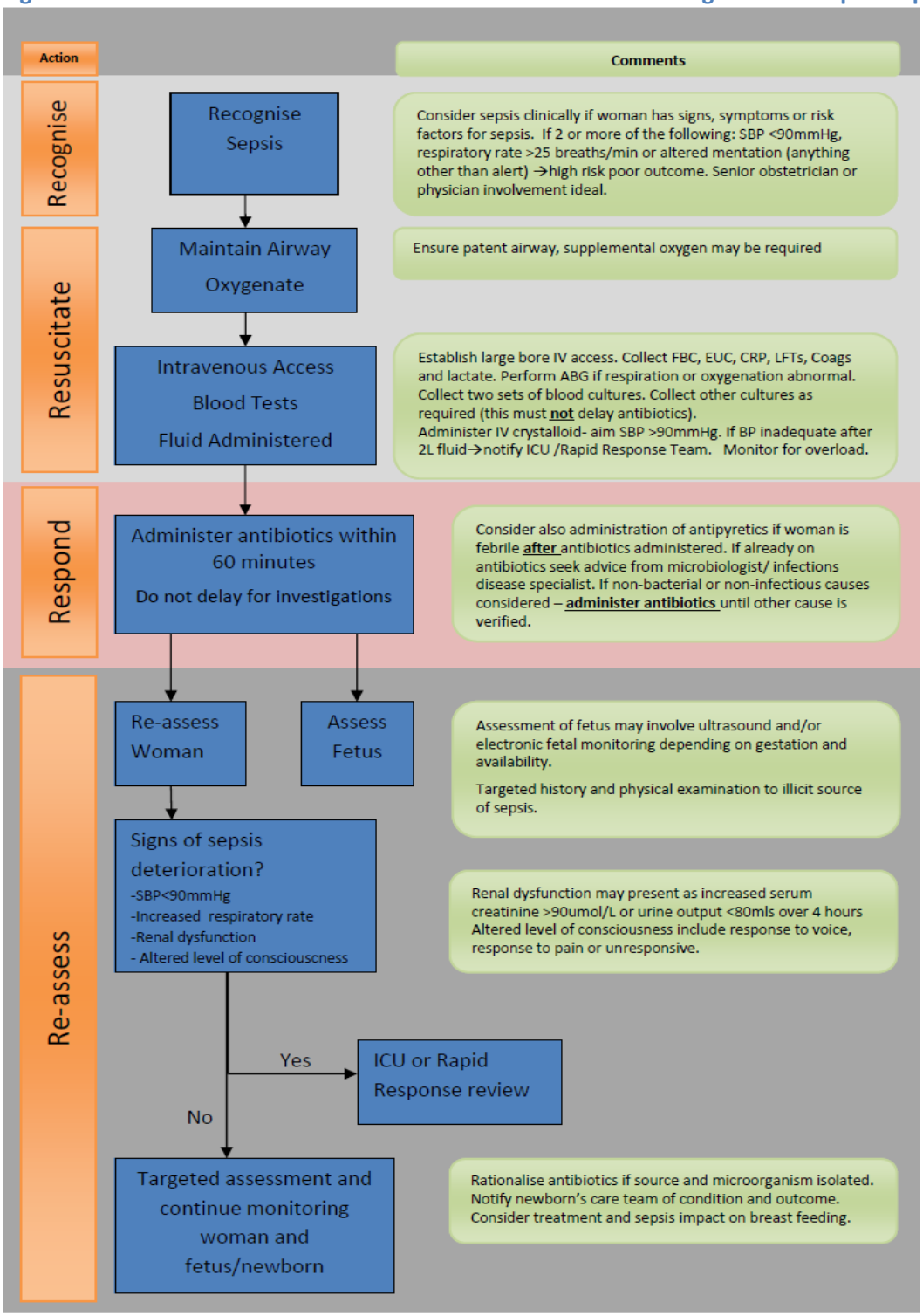
System Parameter	Score				
	0	**1**	**2**	**3**	**4**
Respiration PaO_2/FIO_2	≥400	300 - <400	<300	<200 (with respiratory support)	<100 with respiratory support
Coagulation Platelets,$x10^6$/L	≥150	<150	<100	<50	<20
Liver Bilirubin (µmol/L)	≤20	20-32	33-101	102-204	>204
Cardiovascular Mean Arterial Pressure(mm Hg)	MAP≥70mmHg	MAP<70mmHg	Dopamine <5 or dobutamine (any dose)	Dopamine 5.1-15 or adrenaline <0.1 or noradrenaline <0.1	Dopamine >15 or adrenaline >0.1 or noradrenaline >0.1
Central Nervous System Glasgow Coma Scale	15	13-14	10-12	6-9	<6
Renal Creatinine (µmol/L)	≤110	110-170	171-299	300-440	≥440
Urine output (mL/d)				<500	<200

FIO_2 fraction of inspired oxygen, PaO_2 partial pressure of oxygen, MAP mean arterial pressure, Catecholamine doses expressed as µg/kg/min for at least 1 hour. Adapted from Vincent *et al*[1].

Appendix 2

The flow chart (Figure 1) summarizes the clinically significant steps in the assessment and management of sepsis in pregnancy. The steps are noted in blue boxes and comments relating to the steps are in neighboring green boxes. The relevant section in the guideline relating to each step is in adjacent red boxes.

Figure A2.1: Flowchart and checklist for the assessment and management of sepsis in pregnancy



1. Recognise Sepsis

Calculate omqSOFA
☐ 0 ☐ 1 ☐ ≥2

Is Score ≥ 2?
☐YES (Involve senior obstetrician or physician)
☐NO

TABLE 1 Obstetrically modified qSOFA score

Parameter	Score 0	1
Systolic blood pressure	≥90 mmHg	<90 mmHg
Respiratory rate	Less than 25 breaths/min	25 breath/min or greater
Altered mentation	Alert	Not alert

Min, minute; mmHg, millimetres of mercury; qSOFA, quick Sequential (sepsis-related) Organ Failure Assessment score.

TABLE 2 Obstetrically modified SOFA score

System parameter	Score 0	1	2
Respiration			
PaO_2/FIO_2	≥400	300 to <400	<300
Coagulation			
Platelets, $\times 10^6$/L	≥150	100–150	<100
Liver			
Bilirubin (μmol/L)	≤20	20–32	>32
Cardiovascular			
Mean arterial pressure (mmHg)	MAP ≥ 70	MAP < 70	Vasopressors required
Central nervous system	Alert	Rousable by voice	Rousable by pain
Renal			
Creatinine (μmol/L)	≤90	90–120	>120

FIO_2, fraction of inspired oxygen (expressed as a decimal); MAP, mean arterial pressure; mmHg, millimetres of mercury; PaO_2, partial pressure of oxygen (in mmHg); SOFA, Sequential (sepsis-related) Organ Failure Assessment score.

2. Resuscitate

☐ **Maintain airway**

☐**Consider supplemental oxygen**

☐ **IV access – 2 large bore** (≥18g) cannulas

☐ **Send bloods**
(FBC, UEC, CRP, LFT, COAGS, Lactate)

☐**ABG if respiration or oxygenation abnormal**

☐ **2 sets of blood cultures**

☐ **SEPTIC Screen as indicated**
- Urine MCS
- Vaginal swabs MCS
- Sputum MCS
- Stool MCS

3. Respond

☐**Administer IV antibiotics within 60 minutes**
(Follow local guideline for antibiotic guidance)

☐**Consider antipyretics if febrile AFTER antibiotics**

☐ **Administer IV crystalloid** (Aim SBP >90)

Is BP <90 SBP after 2L IV fluids?
☐ YES (call ICU) ☐ NO

4. Re-assess

☐ **History**
- Targeted to elicit cause of sepsis

☐ **Examination**
- Targeted to elicit cause of sepsis

Calculate omSOFA

SCORE = _____

Are there signs of deterioration
☐ YES (call ICU) ☐ NO
- SBP <90
- RR >25
- Renal dysfunction (Cr>90 or urine output <80ml/4hours)
- Altered mentation

Fetal assessment
☐Ultrasound for growth and welfare
☐CTG

☐ **Notify newborn care**

☐**Consider antibiotic use with breastfeeding**

Created by Anne O'Connor with the assistance of the authorship group

Appendix 3

The q(quick) SOFA (Sequential (sepsis related) Organ Failure Assessment) score is detailed in Table A3.1. The qSOFA criteria allows for prompt, bedside assessment of patients with suspected infections who have sepsis. The patients with sepsis are more likely to have a prolonged ICU stay or increased mortality[14].

Table A3.1: The qSOFA criteria and scores.

Parameter	Score	
	0	1
Systolic Blood Pressure	>100mmHg	≤100mmHg
Respiratory Rate	<22/min	≥22/min
Altered mentation	Alert	Altered mentation

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