Maternity - Sepsis Guideline

Contents

1. Overview

Purpose

The purpose of this document is to provide guidance to identify and treat sepsis in women during pregnancy, birth and postpartum, including miscarriage and termination. This guideline is designed to enable timely care; it does not replace clinical judgment.

Scope

All staff and maternity access holders involved in the care of women with suspected or confirmed sepsis.

Definition

Sepsis is a 'life-threatening condition that arises when the body's response to an infection injures its own tissues and organs' (Czura 2011).

Septic shock is defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone.

2. Background

The Perinatal and Maternal Mortality Review Committee (PMMRC) reported in 2017 that the maternal mortality ratio from 2006-2015 was 16.7 per 100,000 women. Of all the women who died during this period, 13.3% died from either obstetric or non-obstetric sepsis. The PMMRC has noted in the past that sepsis is a cause of maternal death with 50% of sepsis cases attributed to Group A Streptococcal infections.

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3. Prevention of sepsis

Prevention of sepsis in the first instance is a priority. These measures should include:-

- Promotion of and easy access to flu vaccinations
- Excellent hand hygiene practices – *refer to WDHB Hand Hygiene policy*
- Identification and isolation for women who may have known or suspected communicable diseases - *Refer to WDHB Transmission Based Precautions policy*

4. Risk factors and potential causes

Suspect infection - suspect sepsis

In women presenting with signs or symptoms that indicate possible infection, think ***'could this be sepsis?'***
Use a structured set of observations in a face-to-face setting to:

- stratify if sepsis is suspected
- assess the urgency and seniority of obstetric assessment
- assess urgency of treatment

4.1 Identification of risk factors for sepsis

- BMI >30
- Prolonged (>18 hours) rupture of membranes
- Invasive procedures within the previous 6 weeks, for example, amniocentesis, chorionic villus sampling (CVS) and cervical cerclage
- Impaired glucose tolerance/diabetes
- Immunosuppressant, disease or medication
- Recent pelvic infection
- History of Group B Streptococcal infection in current and previous pregnancies
- Group A Streptococcus infection in close contacts/family members
- Low socio-economic status
- Poor antenatal care

4.2 Identification of potential cause of infection

Common obstetric/gynaecological causes:

- Chorioamnionitis/endometritis (uterine)
- Infected caesarean or perineal wound
- Breast abscess/mastitis
- Intrauterine devices/contraceptive implants

Common non-gynaecological causes:

- Urinary tract infection
- Upper or lower respiratory tract infections
- Abdominal causes
- Device-related infection (IV access)

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4.3 Listeria infection in pregnancy

Listeriosis is predominantly a foodborne illness, with the incidence in pregnancy being approximately 13 times higher than the general population. In pregnancy, listeriosis is a serious infection due to the risk of fetal death, premature birth or infection in the neonate. It can occur at any time during pregnancy.

Maternal infection most commonly presents as a non-specific flu-like illness with fever, myalgia, backache and headache, often preceded by diarrhoea or other gastrointestinal symptoms.

Listeriosis should be considered in any pregnant woman with potential exposure to L.monocytogenes presenting with the above symptoms for which no other cause is suspected or found. Blood cultures should be taken and **amoxicillin 2g IV Q6H** started promptly.

4.4 Group A Streptococcal sepsis

- Group A Streptococcal infection can develop rapidly and fulminate into sepsis associated with mortality.
- There should be a high clinical index of suspicion in women presenting acutely unwell with marked leucocytosis, hypotension and tachycardia.
- It should also be suspected in women presenting with sepsis who are not clinically improving despite treatment with standard antibiotic regime.
- Risk factors include recent sore throat or upper respiratory tract infection, premature rupture of membranes, and caesarean section.
- **Benzylpenicillin 1.8g (3MU) IV Q4H** is the recommended antibiotic treatment.
- Consider combination therapy with **clindamycin 600mg IV Q6H** in the case of septic shock after discussion with Infectious Diseases team.
- The Infectious Disease team should be notified and consulted.

If no obvious source of infection can be identified, and there is still high clinical concern in the absence of obvious risk factors, further investigations should be considered.

5. Investigations

Bloods	Other investigations	Imaging
• Full blood count • Two sets blood cultures • C-reactive protein • Urea and creatinine • Liver function tests • Clotting screen • Consider blood gas and lactate	• Midstream urine • Vaginal or perineal swab • Wound swab (Caesarean or perineum) • Nasopharyngeal swab (For Influenza) • Breast milk culture/nipple swab • Other (e.g. sputum, cerebrospinal fluid)	• Chest X-ray • Abdominal X-ray • Pelvic/abdominal ultrasound • CT chest, abdomen and pelvis

- The need for imaging should be led by clinical indication and not withheld due to concerns about radiation exposure to the fetus alone
- Liaise with the general surgical team early if intra-abdominal or pelvic infection is identified on imaging and surgical management is required
- Remember to consider other differential diagnoses

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6. Risk criteria for sepsis

Use the woman's history and physical examination result to complete a sepsis screen.

Women with a confirmed or suspected infection and significant risk factors have a high risk of poor outcomes. Clinical teams should respond with urgency.

Mental status	**High risk criteria**
Interpret a person's mental state in the context of their normal function and treat changes as significant Be aware that changes in cognitive function may be subtle and assessment should include history from woman and family/ carers	Responds only to voice or pain/ unresponsive
Blood Pressure	**High risk criteria**
A drop in systolic blood pressure, especially if accompanied with clammy or sweaty skin should raise concern	SBP ≤90 mmHg
Respiratory	**High risk criteria**
Consider that if peripheral oxygen saturation is difficult to measure in a person with suspected sepsis, this may indicate poor peripheral circulation or poor cardiac output – Consider use of ear probes – Consider arterial blood gas	Respiratory rate ≥25 per min OR Needs oxygen to keep SpO_2 ≥92% *(Note: In non-pregnant population, RR≥22/minute is considered abnormal)*
Circulation	**High risk criteria**
Interpret the heart rate of a person with suspected sepsis in context, taking into account that baseline heart rate in pregnancy is 10–15 beats per minute more than normal Postpartum a heart rate of more than 90 per minute represents tachycardia	Heart rate ≥130/min
Renal function	**High risk criteria**
A low urine output <25ml/hour indicates renal impairment/acute kidney injury due to sepsis Urine output and fluid balance should guide fluid resuscitation Remember that creatinine can be elevated in severe sepsis, and this may be overlooked as creatinine levels are lower in pregnancy than the non-pregnant population. Creatinine levels of >100micromol/L in a pregnant woman should raise concern.	No urine output for >18 hours or <10 mL/hour if catheterised
Temperature	**High risk criteria**
Temperature on its own is not a reliable sign of sepsis. Elicit history of fevers or rigors from the woman or family/care givers Consider that a rise in temperature can be a physiological response, for example after surgery, trauma, lactogenesis, or misoprostol administration.	Tympanic temperature of <36°C or >38°C

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7. Maternity sepsis plan

Signs of sepsis in pregnancy/puerperium are often masked by normal physiology of pregnancy leading to delay in diagnosis. Late detection results in an increased risk of poor outcomes.

By following steps 1-7 below in the first hour, you can double the woman's chance of survival.

8. Treatment

Maternity sepsis plan	
1. Medical assessment	Call for registrar/consultant review, ideally within 30 minutes.
2. Oxygen	Administer oxygen to keep SpO_2 in range 92-96%
3. Bloods and cultures	Aseptic insertion of 16G IV and collect samples prior to antibiotic administration
4. Antibiotics	**Do not wait for investigation results prior to administering antibiotics**
5. IV fluids	Give 1L Plasmalyte or Sodium Chloride 0.9% STAT
6. Urine output and fluid balance	Insert urinary catheter and measure urine output hourly
7. Escalate	If not responding to treatment, vital signs deteriorate, or continued clinical concern: • Notify O&G Specialist immediately • Contact ICU registrar to review 021 494 920 • Contact Critical Care Outreach NSH 021 924 311 / WTK 021 871 733

- Identify and treat the source of sepsis. Once the cause of sepsis has been identified, antibiotics should be prescribed in accordance with the table below. Empiric treatment should be reviewed daily and once a pathogen has been identified antimicrobial therapy should be modified accordingly.
- In the high risk group, prompt treatment with empiric antibiotics within one hour of reviewing the woman is critical to reduce the risk of maternal mortality.
- Consider the safety profile of antibiotics in pregnancy and breastfeeding before administration – see Appendix 3.
- Review choice of antibiotics once microbiology results are known.
- Contact the Infectious Disease team if the woman does not improve despite 48 hours of antibiotics or in the management of complex patients.

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8.1 Antimicrobials

Condition	Antibiotic Regime	Notes
Puerperal sepsis, Pelvic Inflammatory Disease (PID), Chorioamnionitis	Cefuroxime 1.5g IV Q8H + Metronidazole 500mg IV Q12H *Severe penicillin allergy or cephalosporin allergy – discuss with ID*	If haemodynamically unstable the addition of gentamicin may be appropriate. Use 5-7mg/kg (IBW) STAT# and then discuss with ID
Skin and Soft tissue - Surgical Site Infection/Cellulitis e.g. LSCS wound infection **For perineal wound**	Flucloxacillin 2 g IV Q6H *Mild penicillin allergy: Cephazolin 2g IV Q8H* *Severe penicillin allergy: Vancomycin* – dose as per Vanculator* Cefuroxime 1.5g IV Q8H + Metronidazole 500mg IV Q12H	If MRSA colonised – Vancomycin* and discussion with ID See Skin and Soft Tissue Infections – Adults guideline for further information
Skin and soft tissue - Mastitis/Breast abscess	Flucloxacillin 2 g IV Q6H *Mild penicillin allergy: Cephazolin 2g IV Q8H* *Severe penicillin allergy: Vancomycin* - dose as per Vanculator*	If MRSA colonised – Vancomycin* and discussion with ID See Skin and Soft Tissue Infections – Adults guideline for further information
Urinary	Cefuroxime 1.5 g IV Q8H *Severe penicillin allergy or cephalosporin allergy: Gentamicin 5mg/kg IBW IV STAT#, then discuss with ID*	If ESBL colonised - Meropenem 1g IV Q8H and discussion with ID
Respiratory - Bacterial Pneumonia	Amoxicillin/clavulanic acid 1.2 g IV Q8H *Mild penicillin allergy: Cefuroxime 1.5g IV Q8H* *Severe penicillin allergy: Discuss with ID*	If community acquired pneumonia add Azithromycin 500mg PO daily If hospital acquired pneumonia consider multi-drug resistant organism colonisation and discuss with ID
Respiratory - Influenza	Oseltamivir 75mg PO BD	High risk of complications caused by influenza, early treatment is recommended. Benefit is greatest when oseltamivir is initiated within 72 hours of symptom onset

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CNS - Bacterial Meningitis	Antibiotic guidelines for adults (consider risk of Listeria in pregnancy)	
Acute abdominal infection - appendicitis, cholecystitis, diverticulitis	Cefuroxime 1.5g IV Q8H + Metronidazole 500mg IV Q12H *Severe penicillin allergy or cephalosporin allergy: Ciprofloxacin 400mg IV Q12H + Metronidazole 500mg IV Q12H*	If ESBL colonised – Meropenem 1g IV Q8H and discussion with ID
Acute abdominal – suspected perforation	Amoxicillin 1g IV Q6H + Gentamicin 5-7mg/kg (IBW) STAT# + Metronidazole 500mg IV Q12H *Penicillin allergy – discuss with ID*	If ESBL colonised – Meropenem 1g IV Q8H and discussion with ID

#See Appendix 2 for Gentamicin prescribing and monitoring

*See Vancomycin (adults) guideline for dosing and monitoring. Requires ID approval.

8.2 Treatment for suspected sepsis of unknown origin

The below table is for when the source of suspected sepsis is unknown, however the recommendations are not optimal for CNS infections or listeriosis and should therefore be used cautiously in maternity patients.

First line treatment	Notes
Cefuroxime 1.5g IV Q8H + Metronidazole 500mg IV Q12H + Gentamicin 5-7mg/kg (use IBW) STAT# *Severe penicillin allergy or cephalosporin allergy – discuss with ID*	IF ESBL colonised – Meropenem 1g IV Q8H and discuss with ID Not optimal for CNS infections or listeriosis, if suspected discuss with ID.

#See Appendix 2 for Gentamicin prescribing and monitoring

- After an initial dose of gentamicin is given all patients require prompt discussion with ID and therapeutic monitoring is to be initiated. See appendix 2 for more information.
- Patients with renal impairment (CrCl ≤66ml/min) will require a dose reduction. Discuss these patients with ID.

Note: Empiric treatment should be reviewed daily. Once the source and/or pathogen has been identified, antibiotic therapy should be appropriately modified. Please contact ID for advice regarding the management of complex patients.

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9. Thromboprophylaxis

- Pregnancy and sepsis are both status of hypercoagulability, and therefore risk factors for venous thromboembolism
- Consider:
  - Compression stockings/sequential compression device (SCD)
  - Maintenance of hydration
  - Encourage mobilising
  - Use of prophylactic dose of **enoxaparin**

10. Consideration of fetus and timing of birth

Fetal monitoring

- Maternal and placental circulation may be affected by sepsis resulting in fetal compromise
- The fetus should be monitored using cardiotocography (CTG) or ultrasound scanning depending on the clinical situation and gestation. A plan of CTG frequency should be outlined clearly.
- Fetal blood sampling and fetal scalp clips are a relative contraindication in the labouring woman with suspected sepsis
- Inform the Paediatric team, they should be present at the birth in a mother with sepsis

Timing of birth

- Birth timing should be made by an obstetrician considering:
  - Presence of intrauterine sepsis
  - Severity of maternal symptoms and response to initial treatment
  - Current gestation
  - Fetal well-being
- Corticosteroids are not contraindicated in sepsis for preterm gestations, but they should be used with caution, do not delay delivery for steroid administration if there is compromise of the mother or baby
- In extra-uterine sepsis, sepsis treatment should continue to allow prolongation of gestation, unless delivery is thought to be beneficial for the mother, baby or both.

11. References

1	Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche J, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent J, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287
2	PMMRC 2017. 11th Annual Report of the Perinatal and Maternal Mortality Review Committee: Reporting mortality 2015. Wellington: Health Quality & Safety Commission
3	Royal College of Obstetricians and Gynaecologist.2012.Sepsis in pregnancy, bacterial. Green-top guideline No.64a.London, United Kingdom.
4	Cordioli R, Cordioli E, Negrini R, Silva E. Sepsis and pregnancy: do we know how to treat this situation. Rev Bras Ter Intensiva. 2013; 25(4):334-344.
5	Czura CJ, "Merinoff Symposium 2010:Sepsis – Speaking with One voice
6	Maternal Morbidity Working Group Annual Report – 2016-2017 Sepsis pages 11-15

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Appendix 1: Sepsis in pregnancy poster

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Appendix 2: Gentamicin prescribing

Gentamicin belongs to the antibiotic class of aminoglycosides. Aminoglycosides are rapidly bactericidal antimicrobial agents primarily active against Gram-negative bacilli. The role of gentamicin in the treatment of maternal sepsis is well described however due to the narrow therapeutic index of aminoglycosides, and the physiological changes that occur in pregnancy and post-partum, careful consideration must be given to dosing and monitoring.

Initial Dose – Only ONE dose of gentamicin may be prescribed before discussion with Infectious Diseases

5-7*mg/kg STAT based on IDEAL BODY WEIGHT
*Patients with severe sepsis may have higher volumes of distribution and therefore may require a higher initial mg/kg dose.

- Ongoing dosing will be determined by therapeutic drug monitoring
- Exceptions for use of IDEAL BODY WEIGHT:
    - If actual body weight < ideal body weight, then use ACTUAL BODY WEIGHT
    - If actual body weight > 1.25 x ideal body weight, then use ADJUSTED BODY WEIGHT
- Patents with renal impairment (CrCl ≤66ml/min) will require a dose reduction. Please discuss these patients with ID

Therapeutic Drug Monitoring

After an initial dose of gentamicin is given all patients require prompt discussion with ID and therapeutic drug monitoring to be initiated. Ongoing dosing of gentamicin is only indicated for the directed treatment of infections due to gram-negative organisms not able to be treated with alternative agents due to allergies or resistance.

Two serum levels must be taken:

- Peak Level : 1 hour after the dose is given (e.g. if dose is given at 0600hrs via a 30minute infusion, peak level should be taken at 0700hrs)
- Random Level: Any time between 6-14 hours after the dose

Levels will need to be interpreted via a clinical pharmacist (contact the Inpatient Pharmacy or on-call pharmacist outside of business hours), who will provide ongoing dosing advice in consultation with ID.

Calculations

Cockcroft-Gault Equation (to calculate estimated Creatinine Clearance):

$$\text{CrCl (ml/min)} = \frac{F \times (140 - \text{age}) \times \text{weight (kg)}^*}{0.814 \times \text{SrCr}(\mu\text{mol/L})^{\#}}$$

F =0.85 for females
*ideal body weight (kg) (actual or adjusted body weight as per exceptions above)
#wherever possible use a serum creatinine measured within the last 12-24 hours

Ideal Body Weight
IBW (kg) = 45.5 + 0.9 kg/cm over 150cm
Adjusted Body Weight
ABW (kg) = ideal body weight + 0.4(actual body weight – ideal body weight)

Additional details regarding dosing, monitoring, administration and adverse effects of aminoglycosides can be found in the Aminoglycoside Intravenous Dosing and Monitoring – Adults guideline**.**

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Appendix 3: Antimicrobial risk summary in pregnancy and breastfeeding

The tables below are intended to assist the prescriber in determining the level of risk of a specific antimicrobial when prescribed for suspected sepsis in pregnancy or breast feeding. In all instances the below information should be interpreted in the context of the patient and benefits balanced with risks.

Pregnancy Risk Summary

Drug	Category	Risk Summary
Amoxicillin	A	Widely used and generally considered low risk. Some suggestion that exposure during organogenesis is associated with oral clefts. However, even if the association is causal, the absolute risk is very low.
Amoxicillin/clavulanic acid	B1	Widely used however possible association with necrotizing enterocolitis in newborns (related to clavulanic acid) and oral clefts when exposed in 1st and 3rd trimester (see amoxicillin)
Azithromycin	B1	Human data does not suggest risk
Cefuroxime	B1	No detectable teratogenic risk, considered low risk
Cephazolin	B1	No detectable teratogenic risk, considered low risk
Ciprofloxacin	B3	Shown to cause arthropathy in animal data. A number of birth defects have occurred in humans however the lack of pattern is reassuring; a causal relationship cannot be excluded. Should be used with caution, especially in 1st trimester.
Flucloxacillin	B1	Considered low risk
Gentamicin	D (but frequently used in sepsis)	Human data suggests low risk. Benefit outweighs risk in sepsis
Meropenem	B2	Limited human data – animal data suggests low risk
Metronidazole	B2	Human data suggests low risk. Benefit outweighs risk in sepsis
Oseltamivir	B1	Limited human data does not suggest significant risk
Vancomycin	B2	Considered low risk

Breastfeeding Risk Summary

Whenever antibiotics are prescribed to a breast feeding woman, the infant should be monitored for any adverse effects such as rash or gastrointestinal disturbance

Drug	Recommendation	Additional Notes
Amoxicillin	Compatible	Excreted into breast milk in low concentrations.
Amoxicillin/clavulanic acid	Compatible	Excreted into breast milk in low concentrations.
Azithromycin	Compatible	Accumulates in breast milk but considered compatible
Cefuroxime	Compatible	Excreted into breast milk in low concentrations.
Cephazolin	Compatible	Excreted into breast milk in low concentrations.
Ciprofloxacin	Limited human data – potential toxicity, some sources consider compatible	Data is limited, but the concentration in breast milk does not appear to represent significant risk to the infant especially if breast feeding is withheld for several hours after a dose.

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Flucloxacillin	Compatible	Excreted into breast milk in low concentrations.
Gentamicin	Compatible	Excreted into breast milk in low concentrations.
Meropenem	Limited human data – probably compatible	Excreted into breast milk, until additional data available monitor infants for more common adverse effects in adults (headache, gastrointestinal, anaemia, rash).
Metronidazole	Limited human data - potential toxicity but generally considered compatible	Mutagenic and carcinogenic in some animal studies indicating unnecessary exposure should be avoided. However there are no reports of adverse effects in metronidazole exposed nursing infants. Excreted into breast milk in doses that are less than those used to treat infections in infant. Avoid high single-dose therapy.
Oseltamivir	Compatible	Excreted into breast milk in low concentrations
Vancomycin	Limited human data – probably compatible	Excreted into breast milk in low concentrations but poorly absorbed by infant