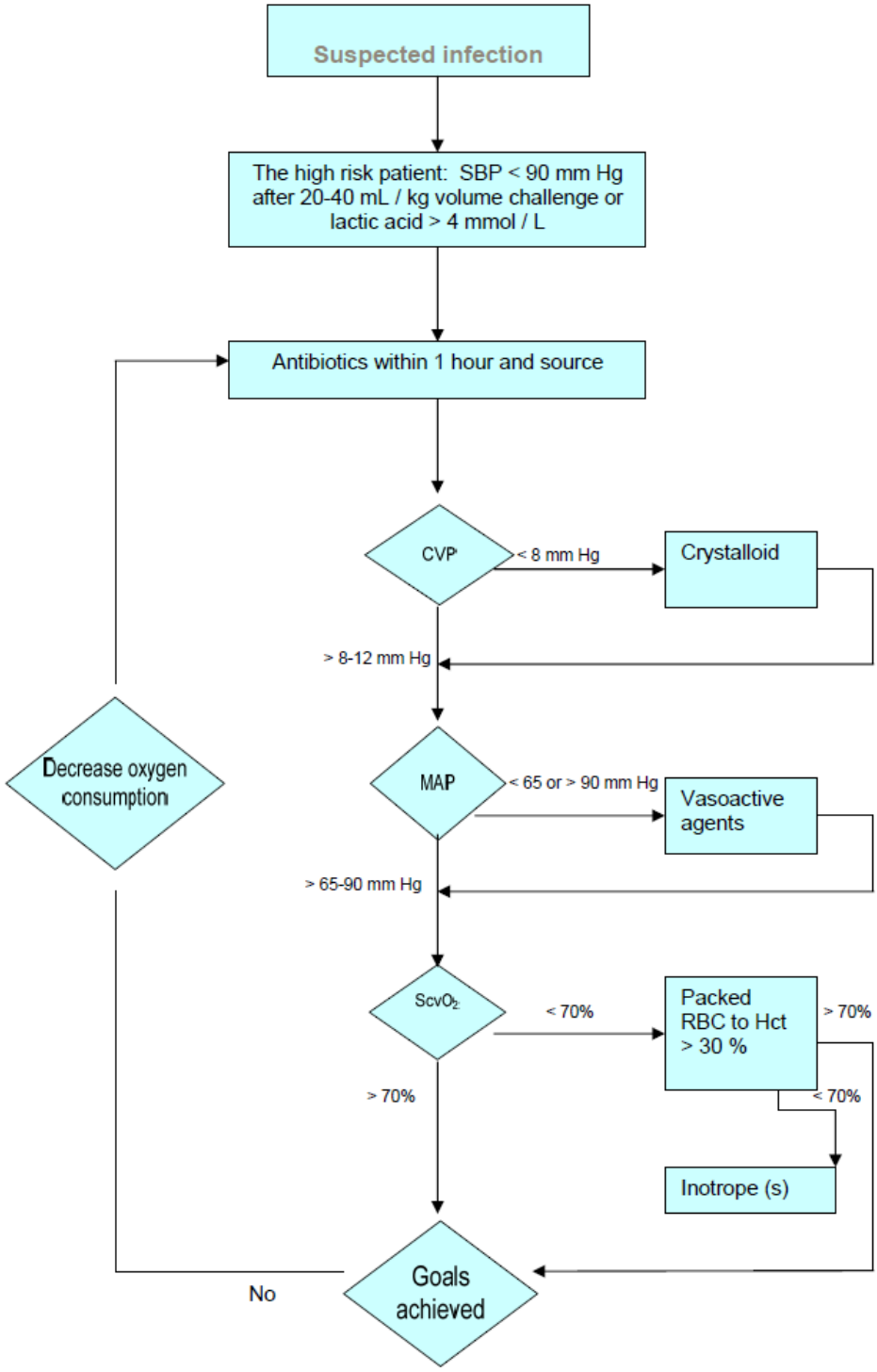
South Australian Paediatric Clinical Guidelines

Sepsis in pregnancy

Early goal directed therapy for sepsis during pregnancy flow chart[1]



ISBN number: 978-1-74243-285-4
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EGDT goals and normal values in pregnancy chart[2]

Measures	Resuscitation goals	Normal third trimester physiologic values
Central venous pressure	8-12 mm Hg	4-10 mm Hg
Mean arterial pressure	≥ 65 mm Hg	84-96 mm Hg
Urine output	> 0.5 mL / kg / hour	Minimum 0.5 mL / kg / hour
Mixed venous oxygen saturation	> 70 %	> 80 %
Heart rate	Decreasing in response to treatment	83 (+/- 10) beats / minute

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The Royal College of Obstetricians and Gynaecologists Green top Guideline 64a - Bacterial sepsis in pregnancy (April 2012) has largely been used to inform this guideline

Introduction

- Sepsis may arise in pregnancy at any time: before delivery, during labour or postpartum. In addition, sepsis may arise from many sources and is not limited to infections arising from the genital tract
- The onset of sepsis may be insidious; women with severe sepsis may appear deceptively well before suddenly collapsing, with little or no warning
- Early identification of severe sepsis allows prompt, appropriate multidisciplinary management
- Suspicion of severe sepsis or septic shock should trigger urgent referral to a tertiary centre with adult intensive care facilities

Definitions

Systemic Inflammatory Response Syndrome (SIRS)

More than one of the following clinical findings:

- Temperature > 38°C or < 36°C
- Heart rate > 90 per minute
- Hyperventilation (evidence by respiratory rate > 20 per minute or PCO_2 < 32 mm Hg
- WCC >12,000 or < 3,000

Sepsis

- Presence of both infection (invasion of tissue, fluid or a body cavity by pathogenic micro-organisms) and systemic manifestations of inflammatory response syndrome (SIRS)

Severe Sepsis

- Sepsis complicated by sepsis-induced organ dysfunction or developing tissue hypoperfusion.

Septic shock

- Persistence of hypoperfusion (hypotension) in a septic patient, despite adequate volume resuscitation
- Hypotension is defined as:
  - Systolic blood pressure (SBP) < 90 mmHg or mean arterial blood pressure (MAP) < 60 mmHg, or reduction of SBP > 40 mmHg from baseline

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- The term puerperal sepsis is used to describe sepsis occurring after delivery and the World Health Organisation (WHO)[8] has defined it as "infection of the genital tract, occurring at any time between rupture of membranes or labour, and the 42nd day postpartum", in which two or more of the following are present:
    - pelvic pain
    - fever
    - abnormal vaginal discharge
    - abnormal smell of discharge
    - delay in postpartum reduction of size of uterus

Literature review

- Up to 20 to 30 % of intensive care unit (ICU) admissions of obstetric patients result from sepsis in pregnancy[10]
- The contribution of sepsis as a cause of maternal mortality is between 3 % in developed countries and 12 % in developing countries[10]
- One third of early maternal mortality is due to refractory hypotension. Late maternal mortality is due to multiple organ failure[10]
- Urinary tract infection and chorioamnionitis are common infections associated with septic shock in the pregnant woman[6]
- In the United Kingdom, the rapid course coupled with late presentation of some women with sepsis have contributed to a recent increase in direct maternal mortality due to genital tract sepsis (especially secondary to Group A streptococcal disease)[4]

Common causes of sepsis in pregnancy

- The most common sites of infection in pregnancy are:
    - Urinary tract (pyelonephritis)
    - Pelvic structures (chorioamnionitis and endometritis)
    - Surgical wounds (caesarean section, perineal laceration)
    - Breast (mastitis)
- Other causes
    - Infection of intravenous cannula sites
    - After urological procedures in the presence of urinary tract infection
    - Related to regional anaesthesia e.g. spinal / epidural abscess (rare)
    - Pneumonia (viral and bacterial)
    - Intrauterine fetal death
    - Septic abortion
    - Acute appendicitis
    - Acute cholecystitis
    - Pancreatitis
    - Necrotising fasciitis

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Common pathogens

- The most prevalent bacterial organisms responsible for severe infection include:
  - Group A beta haemolytic streptococci (GAS), also known as Streptococcus pyogenes
  - Group B streptococcus
  - Escherichia coli
  - Klebsiella
  - Staphylococcus aureus
  - Anaerobes: peptostreptococci, peptococci, bacteroides, clostridium
- Clostridium species and listeria monocytogenes are less common
- Viral causes e.g. influenza, varicella, hepatitis and herpes simplex
- Malaria and other tropical infections

Table 58.1 Common bacterial infections and pathogens related to septic shock[9]

Infections and usual pathogens (in brackets)	Pathogens
Pyelonephritis (1,4) Pneumonia (6,7) Chorioamnionitis (1,2,8-12) Endomyometritis (primarily after caesarean section) (1,2,5,9,12) Sepsis after miscarriage or termination of pregnancy (1,3) Caesarean wound infection (1,2,6,7) Severe mastitis (7) Necrotising fasciitis (2,3,6,9)	1. Escherichia coli 2. Bacteroides 3. Clostridium 4. Klebsiella 5. Pseudomonas aeroginosa 6. Streptococcus species 7. Staphylococcus aureus 8. Group B streptococcus 9. Peptostreptococcus 10. Enterococcus 11. Listeria monocytogenes 12. Enterobacter

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Risk factors for maternal sepsis[12]

As identified by the Confidential Enquiries into Maternal Deaths 2003-2005; 2006-2008

- Obesity
- Impaired glucose tolerance / diabetes
- Impaired immunity / immunosuppressant medication
- Anaemia
- Vaginal discharge
- History of pelvic infection
- History of group B streptococcal infection
- Amniocentesis and other invasive procedures
- Cervical Cerclage
- Prolonged spontaneous rupture of membranes
- Group A streptococcal (GAS) infection in close contacts / family members
- Of black or other minority ethnic group origin[6]

Diagnosis of infection

A thorough history and physical examination is required to make the diagnosis of sepsis. Important elements in making a diagnosis include:

1. Having a suspicion of the diagnosis of sepsis
2. Assessing for evidence of end organ dysfunction
3. Identifying site / source of the infection
4. The speed of onset or deterioration in symptoms and signs is important

Symptoms

- Chills, sweating, warm skin, faintness or syncope, vomiting, rash, headache, dyspnoea, general weakness (or pain related to sites of sepsis – see below)

Signs

One or more of the following:

- Pyrexia (> 38°C): May not always be present and is not necessarily related to the severity of sepsis. Temperature may be < 36°C in severe sepsis
- Tachypnoea (> 20 breaths per minute)
- Hypoxia
- Tachycardia (> 90 bpm)
- Arterial hypotension (systolic blood pressure < 90 mm Hg; mean arterial pressure < 70 mm Hg; or systolic blood pressure decrease > 40 mm Hg)
- Decreased capillary refill or mottling
- Fetal distress secondary to maternal acidosis
- Oliguria (urine output < 0.5 mL / kg / hr for at least two hours, despite adequate fluid resuscitation
- Considerable oedema or positive fluid balance (> 20 mL / kg over 24 hours)

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- Ileus (absent bowel sounds)
- Impaired mental state, altered conscious level
- Hyperglycaemia in the absence of diabetes (plasma glucose > 7.7 mmol / L)
- Bruising or discolouration of skin suggests late fasciitis (often pain receding as cutaneous anaesthesia supervenes as nerves die)
- Failure to respond to treatment

Table 58.2 Assessment for end-organ dysfunction

Acute circulatory failure	> Cardiovascular assessment: Peripheral perfusion, pulse, BP, CVP including signs of high or low cardiac output
Metabolic acidosis	> pH, HCO_3, $PaCO_2$, lactate, anion gap
Acute hypoxaemia	> SpO_2, PaO_2, PaO_2 / FIO_2
Liver dysfunction	> LFTs
Coagulopathy	> CBP and coagulation profile
Acute renal failure	> Fluid overload, urine output > Urea, creatinine, electrolytes
CNS disturbance **e.g. altered mental state**	> Sedation score > AVPU > GCS > Encephalopathy
Overall metabolism	> Assessment for a hyper-catabolic state: negative nitrogen balance (e.g. low albumin) or raised blood glucose levels

Evaluate potential sources of infection

- Identify if any recent sore throat or respiratory illness or close contact with persons with illness (particularly streptococcal infections)
- Exclude intravenous drug misuse (high risk of staphylococcal and streptococcal sepsis)
- Recent febrile illness (especially if associated with chills and rigors -suggest bacteraemia or viraemia)
- Gastrointestinal symptoms (e.g. diarrhoea and vomiting) may be due to food borne pathogens or early toxic shock
- Exclude multiresistant organisms such as ESBL-producing gram negative bacteria, vancomycin-resistant enterococci and MRSA (may affect choice of antimicrobial to combat sepsis and infection control precautions)

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Site of infection – specific considerations

- Early diagnosis to determine if surgical intervention required
- May be difficult to localise the source

Chorioamnionitis

- Uterine tenderness
- Preterm labour +/- PPROM

Endometritis

- Offensive lochia
- Unusual bleeding
- Consider need for evacuation of retained products of conception
- If does not respond to antibiotics, consider septic pelvic thrombosis and commence on heparin

Urinary tract infection

- Loin pain
- Tenderness to renal percussion
- Send MSSU
- Treat acute pyelonephritis aggressively (see PPG, Urinary tract infection)

Mastitis

- Reddened sector in the breast
- Immediate referral to hospital if the woman is clinically unwell, no response to oral antibiotics within 48 hours, mastitis recurs or there are severe or unusual symptoms
- Complications include breast abscess, necrotising fasciitis, toxic shock syndrome

Wound, skin and soft tissue infections

- Signs of inflammation at the site
- Fever, chills, tachycardia, tachypnoea, wound swelling, warm to touch, painful, discharge
- Closed space infections need surgical drainage
- Carefully examine intravenous cannulae or injection sites, and caesarean or episiotomy wounds
- Take a swab of any discharge
- Exclude complications of venous thrombosis or necrotising fasciitis (see below)

Necrotising fasciitis

- Extreme pain in a periphery, associated with signs of prostration and severe sepsis
- Requires early surgical intervention with fasciotomy and aggressive antibiotic treatment

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Bacteraemia and septic shock

- Suspected bacterial sepsis requires careful examination for skin and soft tissue infection
- If drains, vascular access devices or other indwelling devices are suspected as the source of infection, remove as soon as is practicable
- Skin and soft tissue infections are particularly associated with toxic shock syndromes
- Septicaemic seeding of streptococci from a uterine focus may give rise to a secondary focus in a limb, simulating a venous thrombosis
- Women with thrombosis who are systemically unwell with any features of sepsis should be examined very carefully. If shock or other organ dysfunction present, rapid referral to adult intensive care

Pneumonia

- Fever, chills, dyspnoea, cough, sputum production, pleuritic pain
- Consider referral to respiratory physician, medical microbiologist
- Send sputum sample, throat swab for culture
- Chest X-ray

Gastroenteritis

- Diarrhoea and vomiting may be symptoms of bacterial sepsis, due to organisms including staphylococcus and streptococcus
- Stool sample for routine culture (include C. difficile toxin testing if diarrhoea offensive after antimicrobial treatment)
- Salmonella and Campylobacter rarely cause severe systemic infection

Pharyngitis

- Usually viral
- Approximately 10 % of cases are due to GAS
- Obtain throat swab for culture
- Antibiotic treatment if 3 or more of the following: fever, tonsillar exudate, no cough, tender anterior cervical lymphadenopathy

Infection post termination of pregnancy / miscarriage

- Suspect infection in women with a history of a recent termination of pregnancy or spontaneous miscarriage who present with pyrexia, persistent bleeding or abdominal pain, especially if the pain is constant and severe
- Vaginal swabs, ultrasound scan to exclude retained products of conception and consider diagnostic evacuation of uterus (evacuation of retained products of conception) if there is still doubt
- Complete blood picture, C-reactive protein, blood cultures if pyrexia > 38° Celsius
- Commence high dose broad-spectrum intravenous antibiotics without waiting for microbiology results

Cholecystitis / Cholangitis

- Upper right quadrant pain, biliary colic after a fatty meal, jaundice, nausea, vomiting, fever, ultrasonography examination (USG) of abdomen

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Epidural abscess

- Very rare complication
- S. aureus is the usual organism
- Severe backache
- Neurological deficit including bowel / bladder dysfunction and unexplained fever

Investigations

Complete blood picture	> White blood cell (WBC) count > 12 x 10^9 > Leucopenia - WBC count < 4 x 10^9 > Normal WBC count with > 10 % immature forms
Plasma C-reactive protein	> > 7 mg/L (usually significantly higher in bacterial sepsis)
Urea and electrolytes	> Creatinine rise of > 44.2 µmol.L; sepsis is severe if creatinine level > 176 µmol/L
Plasma glucose	> Hyperglycaemia in the absence of diabetes (plasma glucose > 7.7 mmol/L)
Liver function tests (LFTs)	> Hyperbilirubinaemia (plasma total bilirubin > 70 µmol/L)
Coagulation profile	> Coagulation abnormalities (INR > 1.5 or APTT > 60 seconds
Blood gas > Particularly for respiratory tract sepsis but also may detect acidosis from early stage shock	> Arterial hypoxaemia (PaO_2 / FIO_2 < 300 mmHg) > Sepsis is severe if < 250 mmHg in the absence of pneumonia or < 200 mmHg in the presence of pneumonia > Raised serum lactate ≥ 4 mmol/L

Adapted from: RCOG Diagnostic criteria for sepsis (modified from Levy[5])

Depending on the clinical picture:

- Blood cultures (ideally obtain before antibiotic administration)
- Obtain cultures of additional sites as indicated and as soon as possible e.g. micro specimen urine (MSSU), wound swab (episiotomy or caesarean section), placental swabs, respiratory secretions, naso-pharyngeal aspirate (NPA), amniotic fluid, cerebrospinal fluid, HVS, LVS, endocervical, expressed breast milk
- If the methicillin-resistant Staphylococcus aureus (MRSA) status is unknown, obtain swabs from nose, groin and axilla and send for urgent screening
- Suspected pneumonia - Chest X-ray, NPA
- Consider imaging modalities e.g. pelvic ultrasound, computed tomography, magnetic resonance imaging (may help define inflammation or the collection of pus)

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- Echocardiography may be useful in cases of women who are intravenous drug users, particularly those with staphylococcal bacteraemia as there may be right-sided endocarditis and to asses cardiac function

Management

- After identification of severe sepsis, in the first 6 hours, follow the Surviving Sepsis Campaign Resuscitation 'Bundle' (see below)
- Treat underlying infection and support failing organ functions
- Systemically ill patients should commence broad spectrum, intravenous antibiotics (within 1 hour of recognition of severe sepsis)
- Patients with single organ failure not responding to simple measures require transfer to a tertiary centre with high dependency care
- Patients with two or more organ failures and respiratory failure require transfer to a tertiary centre with Level 2 or 3 Adult Intensive Care Facilities (see "Assess for evidence of end-organ dysfunction" above)
- Key Practice Point for outpatients:
  - Abdominal pain, fever (> 38°C), tachypnoea and sustained tachycardia (> 90 beats per minute) are indications for admission and intravenous antibiotics

Table 58.3 Tasks to be performed within the first 6 hours of the identification of severe sepsis[7]

Surviving Sepsis Campaign Resuscitation 'Bundle'

- Obtain blood cultures before antibiotic administration
- Administer broad spectrum antibiotic within one hour of recognition of severe sepsis
- Measure serum lactate
- In the event of hypotension and / or lactate > 4 mmol/L:
  - Deliver an initial minimum 20 mL / kg of crystalloid or an equivalent fluid
  - Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure above 65 mm Hg
- In the event of persistent hypotension despite fluid resuscitation (septic shock) and / or serum lactate > 4 mmol/L:
  - Achieve a central venous pressure (CVP) of ≥ 8 mm Hg
  - Achieve a central venous oxygen saturation ($ScvO_2$) ≥ 70 % or mixed venous oxygen saturation ($ScvO_2$) ≥ 65 %

Adapted from the Surviving Sepsis Campaign Resuscitation Bundle (group of therapies)[13]

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Initial management (0-6 hours)

- Early involvement of senior obstetrician / intensivist / anaesthetist / physician / microbiologist / infectious diseases consultant (as required) with appropriate consultation, referral and retrieval
- Assess need for central venous access and initiate Surviving Sepsis Campaign Resuscitation Bundle if severe sepsis is suspected (see table 58.3 above)
- Follow the A,B,C, D, Es of resuscitation

Airway

- Maintain a clear airway
- Administer oxygen via non-rebreathing mask at 12 litres per minute

Breathing

- Assess breathing pattern, rate and colour and ventilate if required
- Attach pulse oximeter, ECG and automatic BP monitors and monitor SpO_2, maternal pulse and blood pressure

Circulation

- Hypovolaemia is present in almost all patients with septic shock
- Obtain intravenous access
    - Take blood for blood cultures, serum lactate, complete blood count, coagulation profile, urea and electrolytes, liver function tests, blood glucose
- Immediate fluid resuscitation with either crystalloid or colloid as per medical order
    - If no response to simple measures of fluid resuscitation consider the need for insertion of central venous catheter and CVP monitoring
- **Correct hypotension** – Administer vasopressors for hypotension that is not responding to initial fluid resuscitation to maintain mean arterial pressur (MAP) > 65 mmHg (intensivist or anaesthetic management)
- Perform arterial blood gases

Documentation and differential diagnosis

- Obtain history as soon as possible
- Confirm diagnosis
- Commence antibiotic treatment within 1 hour of diagnosis of severe sepsis
- Commence fluid balance chart and monitor urine output

NB: Fluid overload may lead to fatal pulmonary or cerebral oedema in women with septic shock. Clear, accurate documentation and careful monitoring of fluid balance is essential

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Fetal wellbeing

- Assess and monitor fetal wellbeing (cardiotocography) if applicable
- Continuous fetal monitoring intrapartum
- Consider the need for delivery as applicable
    - In a critically ill pregnant woman, birth of the baby may be considered if it would be beneficial to the mother or the baby or to both. A decision on the timing and mode of birth should be made by a senior obstetrician after discussion with the woman if her condition allows
    - If preterm birth is anticipated, cautious consideration should be given to the use of antenatal corticosteroids for fetal lung maturity in the woman with sepsis
    - Epidural / spinal anaesthesia should be avoided in women with sepsis

Observations

- At least hourly vital signs including temperature, pulse, respiratory rate, blood pressure, SpO_2
- Utilise early warning signs chart if available. The use of early warning charts and escalation guidelines including involvement of senior medical staff (intensivist, physician) assists in the early detection and management of the deteriorating patient
- Glasgow Coma Scale and pupil response if required
- Hourly urine output (consider insertion of indwelling catheter)
- In rapidly deteriorating cases, ensure urgent referral to critical care team and obstetric consultant

Antibiotics

- Early consult with microbiologist or infectious diseases consultant for women with evidence of systemic infection
- Commence broad spectrum antibiotic cover within 1 hour of suspicion of severe sepsis, with or without septic shock
- The choice of antibiotic depends on the clinical suspicion, local flora and culture information, if available
- If genital tract sepsis is suspected, prompt early treatment with a combination of high-dose broad-spectrum intravenous antibiotics may be lifesaving
- Empirical treatment should include broad spectrum antimicrobials active against Gram-negative bacteria, and capable of preventing exotoxin production from Gram-positive bacteria (according to local microbiology policy). Gram-positive cover is necessary if the likelihood of this infection is high

Staphylococcal and streptococcal toxic shock syndrome

- Toxic shock syndrome is a life-threatening illness characterised by hypotension and multi-organ failure. It may be caused by Staphylococcus aureus (rarely isolated) or Streptococcus pyogenes that produce and release superantigenic exotoxins. The exotoxins activate T-cells on a large scale resulting in a massive release of inflammatory cytokines[14]

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Staphylococcal toxic shock syndrome	Streptococcal toxic shock syndrome
1. Fever ≥ 39.9°C 2. Rash: diffuse macular erythema 3. Desquamation: 10-14 days after onset of illness, especially palms and soles 4. Hypotension: systolic BP < 90 mmHg	**A. Isolation of group A Streptococcus from:** 1. Normally sterile site: blood, cerebrospinal fluid, peritoneal fluid, tissue biopsy 2. Non-sterile site: throat, vagina, sputum
5. Multisystem involvement: Three or more of the following systems affected: > GIT: vomiting or diarrhoea at onset of illness > Muscular: severe myalgia or elevated creatinine phosphokinase > Mucous membranes: vaginal, oropharyngeal or conjunctival hyperaemia > Renal: creatinine twice the upper limit of normal > Haematological – platelets ≤ 100 x 10^9/L > Central nervous system – disorientation or alterations in consciousness without focal neurological signs	**B. Clinical case definition** Multi-organ involvement characterised by: 1. Hypotension Plus 2. Two or more of the following: > Renal impairment – creatinine > 176 µmol/L > Coagulopathy – platelets < 100 x 10^9/L or disseminated intravascular coagulation > Liver involvement: alanine transaminase or aspartame transaminase or bilirubin levels twice the normal upper limit for age > Acute respiratory distress syndrome > Generalised erythematous macular rash (present in 10 %): may desquamate > Soft tissue necrosis including necrotising fasciitis, myositis or gangrene
Case classification:	**Case classification**
> **Probable:** 4 of the 5 clinical findings positive > **Confirmed:** case with all 5 clinical findings	> **Probable:** meets clinical case definition (above) plus isolation from non-sterile site > **Definite:** meets clinical case definition (above) plus isolation of group A Streptococcus from a normally sterile site

Intravenous immunoglobulin (IVIG)

- IVIG is recommended for severe invasive streptococcal or staphylococcal infection if other therapies have failed
- High dose IVIG has been used in pregnant and postpartum women and is effective in exotoxic shock (i.e. toxic shock attributable to streptococci and staphylococci)[7]
- See PPG, Intragam infusion for more information

Complications

- Acute respiratory distress syndrome (ARDS)
- Disseminated Intravascular coagulation
- Renal failure
- Hepatic failure

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Abbreviations

ARDS	Acute respiratory distress syndrome
AVPU	Alert, verbal, pain, unresponsive
SaO_2	Arterial oxygen satuation
ASAP	As soon as possible
BP	Blood pressure
BSLs	Blood sugar levels
C	Celsius
CBP	Complete blood picture
CNS	Central nervous system
CVP	Central venous pressure
CVS	Cerebro-vascular system
EGDT	Early goal directed therapy
ECG	Electrocardiograph
GAS	Group A beta haemolytic streptococci
GCS	Glasgow coma scale
HCO_3	Bicarbonate ion
HCT	Haematocrit
HVS	High vaginal swab
ICU	Intensive care unit
kg	Kilogram(s)
LFTs	Liver function tests
LVS	Low vaginal swab
MAP	Mean arterial blood pressure
mmHg	Millimetres of mercury
mL	Millimetre(s)
MSSU	Micro specimen of urine
PCO_2	Carbon dioxide partial pressure
PO_2	Oxygen partial pressure
PPROM	Preterm prelabour rupture of the membranes
RBC	Red blood cells
RCOG	Royal College of Obstetricians and Gynaecologists
$ScvO_2$	Central venous oxygen saturation
SpO^2	Oxygen saturation measured by pulse oximetry
SBP	Systolic blood pressure
SIRS	Systemic inflammatory response syndrome
WCC	White cell count
WHO	World Health Organisation

ISBN number: 978-1-74243-285-4
Endorsed by: South Australian Paediatric Clinical Guidelines Reference Committee. South Australian Child Health Clinical Network
Contact: South Australian Paediatric Clinical Guidelines Reference Committee: cywhs.paediatricclinicalguidelines@health.sa.gov.au

Sepsis in pregnancy

Version control and change history

PDS reference: OCE use only

Version	Date from	Date to	Amendment
1.0	20 Nov 12	Current	Original version

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