



Royal College of  
Obstetricians and Gynaecologists

Bringing to life the best in women's health care

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# Bacterial Sepsis in Pregnancy



# Bacterial Sepsis in Pregnancy

This is the first edition of this guideline.

## 1. Purpose and scope

The need for a guideline on the management of sepsis in pregnancy was identified by the 2007 Confidential Enquiry into Maternal Deaths.<sup>1</sup> The scope of this guideline covers the recognition and management of serious bacterial illness in the antenatal and intrapartum periods, arising in the genital tract or elsewhere, and its management in secondary care. Sepsis arising due to viral, fungal or other infectious agents is outside the scope of this guideline. Bacterial sepsis following pregnancy in the puerperium is the subject of a separate Green-top Guideline. The population covered by this guideline includes pregnant women suspected of, or diagnosed with, serious bacterial sepsis in primary or secondary healthcare.

## 2. Background and introduction

Sepsis in pregnancy remains an important cause of maternal death in the UK.<sup>1,2</sup> In 2003–2005 there were 13 direct deaths from genital tract sepsis in pregnancy, five related to pregnancy complications prior to 24 weeks of gestation and eight related to sepsis from 24 weeks of gestation, arising before or during labour. Sadly, substandard care was identified in many of the cases, in particular lack of recognition of the signs of sepsis and a lack of guidelines on the investigation and management of genital tract sepsis.<sup>1</sup> Between 2006 and 2008 sepsis rose to be the leading cause of direct maternal deaths in the UK, with deaths due to group A streptococcal infection (GAS) rising to 13 women.<sup>2</sup> Severe sepsis with acute organ dysfunction has a mortality rate of 20 to 40%, which increases to 60% if septic shock develops.<sup>1</sup> Studies in the non-pregnant population have found that the survival rates following sepsis are related to early recognition and initiation of treatment.<sup>3,5</sup>

Sepsis may be defined as infection plus systemic manifestations of infection. Severe sepsis may be defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion. Septic shock is defined as the persistence of hypoperfusion despite adequate fluid replacement therapy.<sup>3</sup>

## 3. Identification and assessment of evidence

This RCOG guideline was developed in accordance with standard methodology for producing RCOG Green-top Guidelines. The Cochrane Database of Systematic Reviews, DARE, EMBASE, Medline and PubMed (electronic databases) were searched for relevant randomised controlled trials, systematic reviews and meta-analyses. The search was restricted to articles published between 1980 to May 2011. Search terms included: 'sepsis and pregnancy', 'bacterial infection and pregnancy', 'antenatal bacterial infection', 'bacterial sepsis', 'intrapartum septic shock', 'intrapartum infection', 'maternal pyrexia', 'maternal fever', 'systemic inflammatory response syndrome', 'chorioamnionitis', 'genital tract sepsis', 'listeria infection', 'group A *Streptococcus*', '*Streptococcus pyogenes*', '*Streptococcus* and pregnancy', and the search limited to humans and English language. The NHS Evidence, Health Information Resources and the National Guidelines Clearing House were also searched for relevant guidelines and reviews. Studies relevant to the scope of the guideline were selected by the members of the guideline development group. Where possible, recommendations are based on available evidence. Areas where evidence is lacking are annotated as 'good practice points.'

## 4. Which women are at risk of sepsis in pregnancy?

Multiple risk factors for severe sepsis have been identified by the Confidential Enquiries into Maternal Deaths (CEMD) (see table 1).



Risk factors for sepsis identified from the women who died in the 2003-2005 and 2006-2008 triennia are shown in table 1. Many of the women who died had one or more risk factors. Urinary tract infection and chorioamnionitis are common infections associated with septic shock in the pregnant patient.<sup>5</sup>

Evidence level 3

**Table 1. Risk factors for maternal sepsis in pregnancy as identified by the Confidential Enquiries into Maternal Deaths<sup>1,2</sup>**

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
GAS infection in close contacts / family members
Of black or other minority ethnic group origin

## 5. What should prompt recognition of sepsis in the pregnant woman?

**All healthcare professionals should be aware of the symptoms and signs of maternal sepsis and critical illness and of the rapid, potentially lethal course of severe sepsis and septic shock. Suspicion of significant sepsis should trigger an urgent referral to secondary care.**

D

**Clinical signs suggestive of sepsis include one or more of the following: pyrexia, hypothermia, tachycardia, tachypnoea, hypoxia, hypotension, oliguria, impaired consciousness and failure to respond to treatment. These signs, including pyrexia, may not always be present and are not necessarily related to the severity of sepsis.**

D

**Regular observations of all vital signs (including temperature, pulse rate, blood pressure and respiratory rate) should be recorded on a Modified Early Obstetric Warning Score (MEOWS) chart.**

✓

**All staff taking observations should have annual training in the use of the MEOWS chart.**

✓

The signs and symptoms of sepsis in pregnant women may be less distinctive than in the non-pregnant population and are not necessarily present in all cases;<sup>4</sup> therefore, a high index of suspicion is necessary. Clinical features suggestive of sepsis are shown in table 2. Healthcare professionals should be aware of the symptoms and signs of maternal sepsis and critical illness. Disease progression may be much more rapid than in the non-pregnant state. Genital tract sepsis may present with constant severe abdominal pain and tenderness unrelieved by usual analgesia, and this should prompt urgent medical review.<sup>1</sup> Severe infection may be associated with preterm labour. Toxic shock syndrome caused by staphylococcal or streptococcal exotoxins can produce confusing symptoms including nausea, vomiting and diarrhoea; exquisite severe pain out of proportion to clinical signs due to necrotising fasciitis; a watery vaginal discharge; generalised rash; and conjunctival suffusion.

Evidence level 4

Diagnostic criteria for sepsis and severe sepsis are provided in appendix 1 and features of toxic shock syndrome are listed in appendix 2.

**Table 2.** Clinical features suggestive of sepsis. Modified from references 1 and 3.

Fever or rigors
Diarrhoea or vomiting - may indicate exotoxin production (early toxic shock)
Rash (generalised streptococcal maculopapular rash or purpura fulminans)
Abdominal /pelvic pain and tenderness
Offensive vaginal discharge (smelly suggests anaerobes; serosanguinous suggests streptococcal infection)
Productive cough
Urinary symptoms

## 6. What are the appropriate investigations when sepsis is suspected?

**Blood cultures are the key investigation and should be obtained prior to antibiotic administration; however, antibiotic treatment should be started without waiting for microbiology results.**

D

**Serum lactate should be measured within six hours of the suspicion of severe sepsis in order to guide management. Serum lactate  $\geq 4$  mmol/l is indicative of tissue hypoperfusion.**

D

**Any relevant imaging studies should be performed promptly in an attempt to confirm the source of infection.**

D

Blood cultures and other samples as guided by clinical suspicion of the focus of infection (e.g. throat swabs, mid-stream urine, high vaginal swab, or cerebrospinal fluid) should be obtained prior to starting antibiotic therapy as they may become uninformative within a few hours of commencing antibiotics but must not delay antibiotic therapy.<sup>3</sup> If the methicillin-resistant *Staphylococcus aureus* (MRSA) status is unknown, a pre-moistened nose swab may be sent for rapid MRSA screening where such testing is available. The results of these tests should be reviewed when they become available to allow subsequent optimisation of the antibiotic regime. Similarly, prompt imaging may identify the source of the infection, allowing early definitive treatment, and should not be deferred on the grounds of pregnancy.<sup>3</sup>

Evidence level 4

Use of the resuscitation 'bundle' developed as part of the Surviving Sepsis Campaign is recommended (see table 3) and includes measurement of serum lactate **within six hours** of suspicion of severe sepsis with the result being used to guide management.<sup>3</sup> Arterial blood gas measurement should be undertaken to assess for hypoxia. Laboratory findings suggestive of a diagnosis of sepsis are outlined in appendix 1.

**Table 3.** Tasks to be performed within the first six hours of the identification of severe sepsis. Modified from the Surviving Sepsis Campaign Resuscitation 'Bundle' (group of therapies)<sup>3</sup>

Obtain blood cultures prior to antibiotic administration
Administer broad-spectrum antibiotic within one hour of recognition of severe sepsis
Measure serum lactate
In the event of hypotension and/or a serum lactate $>4$ mmol/l deliver an initial minimum 20ml/kg of crystalloid or an equivalent. Apply vasopressors for hypotension that is not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) $>65$ mmHg
In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate $>4$ mmol/l <ol style="list-style-type: none"> <li>Achieve a central venous pressure (CVP) of <math>\geq 8</math>mmHg</li> <li>Achieve a central venous oxygen saturation (ScvO<sub>2</sub>) <math>\geq 70\%</math> or mixed venous oxygen saturation (SvO<sub>2</sub>) <math>\geq 65\%</math></li> </ol>

## 7. Who should be involved in the collaborative care of women with sepsis?

If sepsis is suspected, regular frequent observations should be made. The use of a MEOWS chart is recommended. There should be an urgent referral to the critical care team in severe or rapidly deteriorating cases, and the involvement of a consultant obstetrician.

D

The expert advice of a consultant microbiologist or infectious disease physician should be sought urgently when serious sepsis is suspected.

D

A MEOWS chart should be used for all maternity inpatients to identify seriously ill pregnant women and refer them to critical care and obstetric anaesthetic colleagues according to local guidelines.<sup>1</sup>

Evidence level 3

Early, goal-directed resuscitation has been shown to improve survival for non-pregnant patients presenting with septic shock.<sup>6</sup>

Evidence level 1+

The Surviving Sepsis Campaign Resuscitation Bundle recommends that this is commenced pending transfer to an intensive care unit (ICU).<sup>3</sup> See table 3 for details of the bundle.

The decision to transfer to intensive care should be decided by the critical care team in conjunction with the obstetric consultant and the consultant obstetric anaesthetist.<sup>7</sup> Cardiac output monitoring, ventilatory support requiring intubation, and renal support would all require transfer to ICU in the majority of units (see table 4).

Evidence level 4

**Table 4.** Indications for transfer to ICU. Adapted from Plaat and Wray (2008)<sup>8</sup>

System	Indication
Cardiovascular	Hypotension or raised serum lactate persisting despite fluid resuscitation, suggesting the need for inotrope support
Respiratory	Pulmonary oedema Mechanical ventilation Airway protection
Renal	Renal dialysis
Neurological	Significantly decreased conscious level
Miscellaneous	Multi-organ failure Uncorrected acidosis Hypothermia

## 8. What are the commonly identified organisms, including hospital acquired infection?

The most common organisms identified in pregnant women dying from sepsis are Lancefield group A beta-haemolytic *Streptococcus* and *E.Coli*.<sup>1,2</sup>

Mixed infections with both Gram-positive and Gram-negative organisms are common, especially in chorioamnionitis. Coliform infection is particularly associated with urinary sepsis, preterm premature rupture of membranes, and cerclage.<sup>1</sup> Anaerobes such as *Clostridium perfringens* (the cause of gas gangrene) are less commonly seen nowadays, with *Peptostreptococcus* and *Bacteroides spp.* predominating.<sup>9</sup>

Evidence level 3

## 9. What empirical and specific antimicrobial therapy should be used to treat the woman?

Administration of intravenous broad spectrum antibiotics is recommended within one hour of suspicion of severe sepsis, with or without septic shock.

D

**If genital tract sepsis is suspected, prompt early treatment with a combination of high-dose broad-spectrum intravenous antibiotics may be lifesaving.**

**D**

Administration of intravenous broad spectrum antibiotics are recommended within one hour of suspicion of severe sepsis in the woman, with or without septic shock, as part of the Surviving Sepsis Campaign Resuscitation Bundle.<sup>3</sup>

Empirically, broad spectrum antimicrobials active against Gram-negative bacteria, and capable of preventing exotoxin production from Gram-positive bacteria, should be used according to local microbiology policy, and therapy narrowed once the causative organism(s) has been identified.

Evidence level 4

The 2003–2005 CEMACH report<sup>1</sup> referred to the use of cefuroxime and metronidazole for genital tract sepsis. However, cefuroxime is no longer part of many hospital formularies because of the association with *C. difficile*. Neither agent provides any MSRA, *Pseudomonas* or extended-spectrum beta-lactamases (ESBL) cover (see appendix 3 for range of activity of common antibiotics). Information on antimicrobials which may aid in guiding choice is provided in table 5; however, hospital guidelines differ, and local guidance should be followed as the incidence of resistant organisms varies throughout the UK.

In addition to antimicrobial therapy, the source of sepsis should be sought and dealt with if possible: for example, by delivery of the baby.<sup>1</sup>

Evidence level 3

**Table 5. Antimicrobial choices and limitations of antimicrobial.**

Co-amoxiclav	Does not cover MRSA or <i>Pseudomonas</i> , and there is concern about an increase in the risk of necrotising enterocolitis in neonates exposed to co-amoxiclav in utero. <sup>10</sup>
Metronidazole	Only covers anaerobes.
Clinدامycin	Covers most streptococci and staphylococci, including many MRSA, and switches off exotoxin production with significantly decreased mortality. <sup>11,12</sup> Not renally excreted or nephrotoxic.
Piperacillin–tazobactam (Tazocin) and carbapenems	Covers all except MRSA and are renal sparing (in contrast to aminoglycosides).
Gentamicin (as a single dose of 3–5mg/kg)	Poses no problem in normal renal function but if doses are to be given regularly serum levels must be monitored.

## 10. What is the role of intravenous immunoglobulin (IVIG)?

**IVIG is recommended for severe invasive streptococcal or staphylococcal infection if other therapies have failed.**

**D**

IVIG has an immunomodulatory effect, and in staphylococcal and streptococcal sepsis it also neutralises the superantigen effect of exotoxins, and inhibits production of tumour necrosis factor (TNF) and interleukins. The Department of Health has recommendations regarding the use of IVIG for invasive streptococcal and staphylococcal infection.<sup>13</sup>

Evidence level 4

High dose IVIG has been used in pregnant women<sup>14</sup> and is effective in exotoxic shock (i.e. toxic shock due to streptococci and staphylococci) but with little evidence of benefit in Gram-negative (endotoxin related) sepsis. The main contraindication to IVIG use is a congenital deficiency of immunoglobulin A. Its use in women with severe staphylococcal and streptococcal sepsis should be discussed with infectious disease colleagues or medical microbiologists.

Evidence level 3

IVIG is available from the blood transfusion department, and all commercial brands of IVIG available in the UK contain antibodies to streptococcal and staphylococcal exotoxins. Actual administration of IVIG should

be through a blood warming device, and hospital protocols for replacement therapy in haematology patients may be used.

## 11. How should the fetus be monitored and when and how should the baby be delivered?

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 following discussion with the woman if her condition allows.



If preterm delivery is anticipated, cautious consideration should be given to the use of antenatal corticosteroids for fetal lung maturity in the woman with sepsis.



During the intrapartum period, continuous electronic fetal monitoring is recommended. Changes in cardiotocography (CTG), such as changes in baseline variability or new onset decelerations, must prompt reassessment of maternal mean arterial pressure, hypoxia and acidaemia.



Epidural/spinal anaesthesia should be avoided in women with sepsis and a general anaesthetic will usually be required for caesarean section.



The effects of maternal sepsis on fetal wellbeing include the direct effect of infection in the fetus, the effect of maternal illness/shock and the effect of maternal treatment. The risk of neonatal encephalopathy and cerebral palsy is increased in the presence of intrauterine infection.<sup>15</sup>

Evidence level 2+

If preterm delivery is anticipated the use of antenatal corticosteroids for fetal lung maturity in the woman with sepsis can be considered.<sup>16,17</sup> See RCOG Green-top Guideline No.7, Antenatal Corticosteroids to Reduce Neonatal Morbidity.<sup>16</sup>

Evidence level 4

During the intrapartum period, continuous electronic fetal monitoring is recommended in the presence of maternal pyrexia (defined as a temperature >38.0 °C once, or 37.5 °C on two occasions 2 hours apart)<sup>18</sup> and this should also apply to sepsis without pyrexia.

Objective evidence of intrauterine infection is associated with abnormal fetal heart monitoring; however, electronic fetal monitoring is not a sensitive predictor of early onset neonatal sepsis.<sup>19,20</sup>

Evidence level 2+

Changes in CTG, such as changes in baseline variability or new onset decelerations, must also prompt reassessment of maternal mean arterial pressure, hypoxia and acidaemia. These changes may serve as an early warning sign for derangements in maternal end-organ systems.<sup>17</sup> There is insufficient evidence regarding fetal blood sampling in the presence of maternal sepsis to guide practice.

Evidence level 4

Attempting delivery in the setting of maternal instability increases the maternal and fetal mortality rates unless the source of infection is intrauterine.<sup>21</sup> The decision on mode of delivery should be individualised by the consultant obstetrician with consideration of severity of maternal illness, duration of labour, gestational age and viability.<sup>17</sup>

## 12. What prophylaxis should be considered for the neonate, other family members and healthcare workers?

Local and national guidelines should be followed in consultation with the local health protection unit or lead for communicable disease control.



When a mother has been found to have invasive group A streptococcal infection in the peripartum period, the neonatologist should be informed and prophylactic antibiotics administered to the baby.



Close household contacts of women with group A streptococcal infection should be warned to seek medical attention should symptoms develop, and the situation may warrant antibiotic prophylaxis.



Healthcare workers who have been exposed to respiratory secretions of women with group A streptococcal infection should be considered for antibiotic prophylaxis.



The Health Protection Agency have produced detailed guidelines for the investigation, control and prevention of the spread of group A streptococcal infection in healthcare settings in the United Kingdom.<sup>22</sup>

As well as the specific recommendation for group A streptococcal disease, any baby of a mother found to have sepsis in the peripartum period should be discussed with neonatology colleagues so that prophylactic antibiotic administration to the baby can be considered.<sup>22</sup>

Evidence level 4

### 13. What infection control issues should be considered?

Group A  $\beta$ -haemolytic *Streptococcus* and MRSA are easily transmitted via the hands of healthcare workers and via close contact in households. Local infection control guidelines should be followed for hospital-specific isolation and contact precautions.



Invasive group A streptococcal infections are notifiable and the infection control team and the consultant for communicable diseases should be informed.



Women suspected of or diagnosed with group A *Streptococcus* sepsis should be isolated in a single room with en suite facilities to minimise the risk of spread to other women. Local advice from infectious control colleagues should always be sought.

### 14. Suggested audit topics

- The existence of locally based guidelines for the investigation and management of genital tract sepsis in the maternity unit.
- The use of a version of a MEOWS chart to aid the identification of seriously ill pregnant women<sup>1</sup> in the maternity unit.
- The proportion of pregnant women with suspected severe sepsis who had serum lactate measured within six hours of presentation.



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## APPENDIX 1

Diagnostic criteria for sepsis modified from Levy et al (2003)<sup>23</sup> for pregnant women using references 1 and 2 where pregnancy specific parameters are available.

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### Infection, documented or suspected, and some of the following:

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#### General variables:

Fever ( $>38^{\circ}\text{C}$ )

Hypothermia (core temperature  $<36^{\circ}\text{C}$ )

Tachycardia ( $>100$  beats per minute)

Tachypnoea ( $>20$  breaths per minute)

Impaired mental state

Significant oedema or positive fluid balance ( $>20\text{ml/kg}$  over 24 hours)

Hyperglycaemia in the absence of diabetes (plasma glucose  $>7.7$  mmol/l)

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#### Inflammatory variables:

White blood cell (WBC) count  $>12 \times 10^9/\text{l}$  (note that a transient leucocytosis is common in labour)

Leucopenia (WBC count  $<4 \times 10^9/\text{l}$ )

Normal WBC count with  $>10\%$  immature forms

Plasma C-reactive protein  $>7\text{mg/l}$

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#### Haemodynamic variables:

Arterial hypotension (systolic blood pressure  $<90\text{mmHg}$ ; mean arterial pressure  $<70\text{mmHg}$  or systolic blood pressure decrease  $>40\text{mmHg}$ )

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#### Tissue perfusion variables:

Raised serum lactate  $\geq 4$  mmol/l

Decreased capillary refill or mottling

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#### Organ dysfunction variables:

Arterial hypoxaemia ( $\text{PaO}_2$  (arterial oxygen partial pressure) / $\text{FIO}_2$  (fraction of inspired oxygen)  $<40\text{kPa}$ ). Sepsis is severe if  $<33.3\text{kPa}$  in the absence of pneumonia or  $<26.7\text{kPa}$  in the presence of pneumonia.

Oliguria (urine output  $<0.5\text{ml/kg/hr}$  for at least two hours, despite adequate fluid resuscitation)

Creatinine rise of  $>44.2\mu\text{mol/l}$ . Sepsis is severe if creatinine level  $>176\mu\text{mol/l}$

Coagulation abnormalities (International Normalised Ratio [INR]  $>1.5$  or activated partial thromboplastin time [APTT]  $>60\text{s}$ )

Thrombocytopenia (platelet count  $<100 \times 10^9/\text{l}$ )

Hyperbilirubinaemia (plasma total bilirubin  $>70\mu\text{mol/l}$ )

Ileus (absent bowel sounds)

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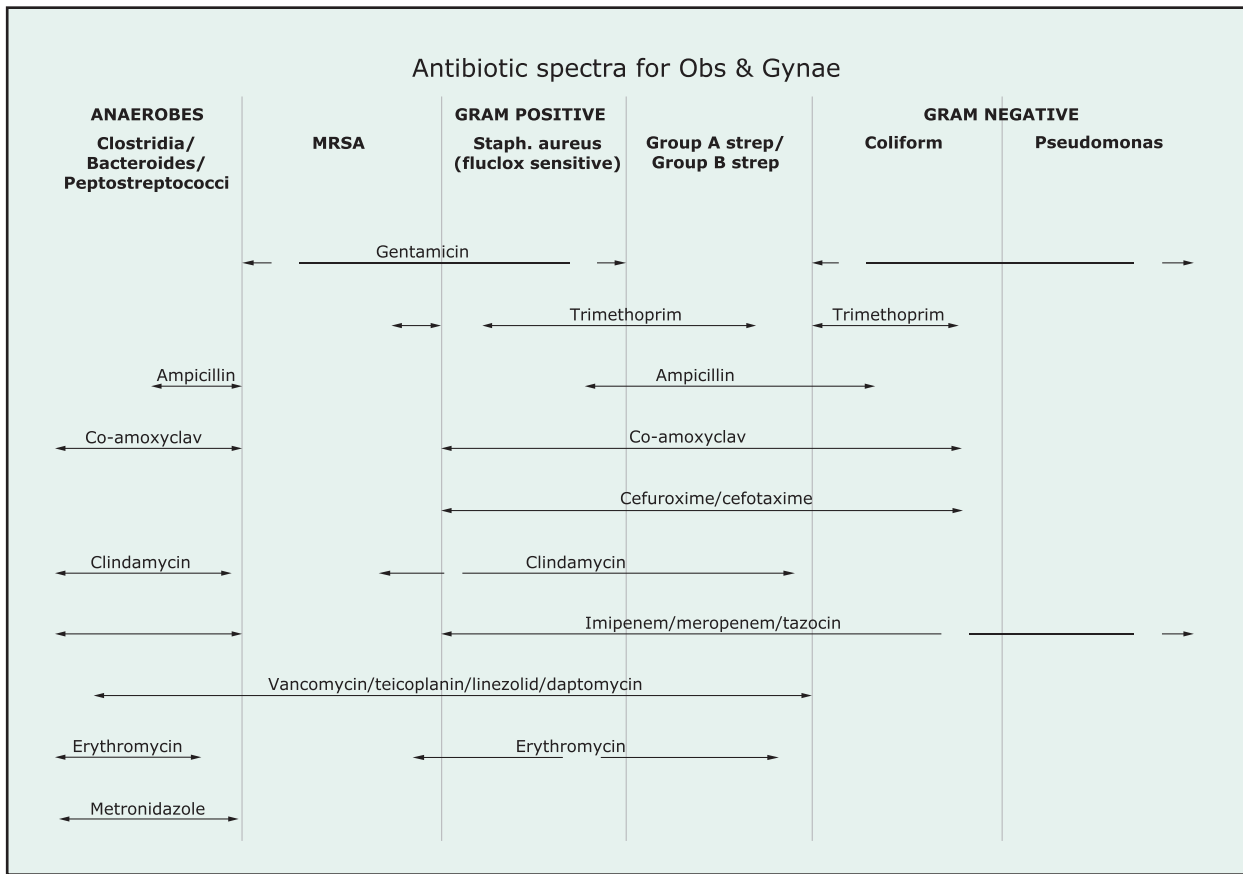
## APPENDIX 2

### Staphylococcal and streptococcal toxic shock syndrome clinical disease definition.<sup>12,23</sup>

Staphylococcal toxic shock <sup>24</sup>	Streptococcal toxic shock syndrome <sup>12,24</sup>
<ol style="list-style-type: none"> <li>1. Fever &gt; / = 39.9°C</li> <li>2. Rash – diffuse macular erythroderma</li> <li>3. Desquamation – 10 to 14 days after onset of illness, especially palms and soles</li> <li>4. Hypotension – systolic BP &lt; 90 mm Hg adults</li> </ol>	<p>A. Isolation of beta-haemolytic group A <i>Streptococcus</i> from:</p> <ol style="list-style-type: none"> <li>1. normally sterile site – blood, CSF, peritoneal fluid, tissue biopsy</li> <li>2. non-sterile site – throat, vagina, sputum</li> </ol>
<p>5. Multisystem involvement</p> <p>Three or more of the following systems affected:</p> <ul style="list-style-type: none"> <li>● Gastrointestinal – vomiting or diarrhoea at onset illness</li> <li>● Muscular – severe myalgia or elevated creatinine phosphokinase</li> <li>● Mucous membranes – vaginal, oro-pharyngeal or conjunctival hyperaemia</li> <li>● Renal – creatinine twice the upper limit of normal</li> <li>● Hepatic – total bilirubin twice the upper limit of normal</li> <li>● Haematological – platelets &lt; / = 100 x 10<sup>9</sup>/l</li> <li>● Central nervous system – disorientation or alterations in consciousness without focal neurological signs</li> </ul>	<p>B. Clinical case definition</p> <p>Multi-organ involvement characterised by:</p> <ol style="list-style-type: none"> <li>1. Hypotension plus</li> <li>2. Two or more of the following: <ul style="list-style-type: none"> <li>● Renal impairment – creatinine &gt;176µmol/l</li> <li>● Coagulopathy – platelets &lt; 100 x 10<sup>9</sup>/l or disseminated intravascular coagulation</li> <li>● Liver involvement – alanine transaminase or aspartame transaminase or bilirubin levels twice the normal upper limit for age</li> <li>● Acute respiratory distress syndrome</li> <li>● Generalised erythematous macular rash (present in 10%) – may desquamate</li> <li>● Soft tissue necrosis including necrotising fasciitis, myositis or gangrene</li> </ul> </li> </ol>
<p><b>Case classification:</b></p> <p><b>Probable</b> – four of the five clinical findings positive</p> <p><b>Confirmed</b> – case with all five clinical findings</p>	<p><b>Case classification:</b></p> <p><b>Probable</b> – meets clinical case definition (above) plus isolation from non-sterile site</p> <p><b>Definite</b> – meets clinical case definition (above) plus isolation of group A <i>Streptococcus</i> from a normally sterile site</p>

### APPENDIX 3

Antibiotic spectra for obstetrics and gynaecology.



*Dr Marina S Morgan, 2012*


Solid lines represent roughly the proportion of the bacteria sensitive to that antibiotic.

NB: Tazocin may not be effective against some ESBL producing Gram-negative bacteria, and carbapenemase producing organisms will be resistant to carbapenems.

## APPENDIX 4

Clinical guidelines are 'systematically developed statements which assist clinicians and women in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No.1: *Development of RCOG Green-top Guidelines* (available on the RCOG website at <http://www.rcog.org.uk/guidelines>). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research might be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels	Grades of recommendations
1++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias	<b>A</b> At least one meta-analysis, systematic review or randomised controlled trial rated as 1++ and directly applicable to the target population; or A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias	<b>B</b> A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
1- Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias	<b>C</b> A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
2++ High-quality systematic reviews of case-control or cohort studies or high-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal	<b>D</b> Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
2+ Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal	
2- Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal	
3 Non-analytical studies, e.g. case reports, case series	
4 Expert opinion	
	<b>Good practice point</b>  Recommended best practice based on the clinical experience of the guideline development group

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The final version is the responsibility of the Guidelines Committee of the RCOG.

The guidelines review process will commence in 2015 unless evidence requires an earlier review.

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