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Bacterial Sepsis following Pregnancy

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This is the first edition of this guideline.

1. Purpose and scope

The purpose of this guideline is to provide guidance on the management of sepsis in the puerperium (i.e. sepsis developing after birth until 6 weeks postnatally), in response to the findings of the Centre for Maternal and Child Enquiries (CMACE) Eighth Report on Confidential Enquiries into Maternal Deaths in the United Kingdom.[1]

This topic is particularly relevant as there has been a dramatic rise in maternal deaths attributable to group A beta-haemolytic streptococci (GAS) (three in 2000–2002[2] and 13 in 2006–2008).[1] The most common site of sepsis in the puerperium is the genital tract and in particular the uterus, resulting in endometritis. This guideline covers the recognition of febrile bacterial illness in the postpartum period – including postabortion sepsis – arising in the genital tract or elsewhere, investigations to identify and characterise sepsis in the puerperium, and management strategies. The population covered includes women in the puerperium (i.e. within 6 weeks of giving birth) with suspected or diagnosed bacterial sepsis in primary or secondary care. Sepsis in pregnancy is covered by a parallel guideline. Sepsis arising owing to viral or parasitic agents is outside the scope of this guideline. This guideline excludes mild to moderate illness in primary care.

2. Background and introduction

Despite significant advances in diagnosis, medical management and antimicrobial therapy, sepsis in the puerperium remains an important cause of maternal death, accounting for around 10 deaths per year in the UK.[1] Severe sepsis with acute organ dysfunction has a mortality rate of 20–40%, rising to around 60% if septicaemic shock develops.[3]

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.[3]

Symptoms of sepsis (see section 7) may be less distinctive than in the non-pregnant population and are not necessarily present in all cases; therefore, a high index of suspicion is necessary.

Disease progression may be rapid. Genital tract sepsis may present with constant severe abdominal pain and tenderness unrelieved by usual analgesia, and this should prompt urgent medical review.[1]

3. Identification and assessment of evidence

This 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 and May 2011. Search terms included: 'postpartum sepsis', 'postpartum infection', 'septic shock, postpartum', 'puerperal sepsis', 'puerperal pyrexia', 'puerperal fever', 'genital tract sepsis', 'bacterial sepsis', 'toxic shock', 'activated protein C and postpartum', '*Streptococcus* infection and puerperium', 'group A streptococcus', '*Streptococcus pyogenes*', 'beta haemolytic *Streptococcus* and puerperium'. The search was limited to humans and the English language. The National Library for Health 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 lacking evidence are highlighted and annotated as 'good practice points' (tick).

4. Who is at increased risk of sepsis in the puerperium?

Multiple risk factors for maternal sepsis have been identified by CMACE (Table 1).[1,2] Many of those who died in the UK CMACE survey 2005–2008 had one or more risk factors.

Table 1. Risk factors for maternal sepsis as identified by the Confidential Enquiries into Maternal Deaths[1,2]

Obesity
Impaired glucose tolerance / diabetes
Impaired immunity / immunosuppressant medication
Anaemia
Vaginal discharge
History of pelvic infection
Amniocentesis and other invasive procedures
Cervical cerclage
Prolonged spontaneous rupture of membranes
Vaginal trauma, caesarean section, wound haematoma
Retained products of conception
GAS infection in close contacts / family members
Black or minority ethnic group origin

Another recognised risk factor for sepsis in the puerperium is acquisition or carriage of invasive organisms, especially GAS.[1,2,4,5]

5. What are the common organisms causing sepsis in the puerperium, including hospital-acquired infection?

The major pathogens causing sepsis in the puerperium are:

- GAS, also known as *Streptococcus pyogenes*
- *Escherichia coli*
- *Staphylococcus aureus*
- *Streptococcus pneumoniae*
- meticillin-resistant *S. aureus* (MRSA), *Clostridium septicum* and *Morganella morganii*.

GAS is increasingly causing invasive infections worldwide and was directly responsible for 13 of the 29 maternal deaths from infection in the UK during 2006–2008.[1]

Since the 2003–2005 survey,[2] MRSA carriage and infection has increased worldwide, with rates of 2.1% reported in mothers in the puerperium in the USA.[6] The CMACE report identified one maternal death from Panton–Valentine leukocidin (PVL)-producing MRSA following caesarean section.[1]

Gram-negative bacteria that produce extended-spectrum beta-lactamases (ESBL) are an increasingly common cause of co-amoxiclav- and cephalosporin-resistant urinary tract infections and caused one of the maternal deaths in the CMACE report.[1] Since 2003, the UK incidence of ESBL-producing bacteria has increased to more than 12% of coliform bacteria.This may have implications for use of cephalosporins for infections in penicillin-allergic women. *Clostridium* spp. remain uncommon causes of death from sepsis in the puerperium, with one case of *C. septicum* reported post-termination of pregnancy.[1]

6. What are the likely causes of sepsis outside the genital tract and how might they be identified?

A general history and examination should be carried out to try and identify the source of sepsis. ✓

Women should be assessed clinically and, if unwell or with dehydration or vomiting, admission should be considered. ✓

Mastitis, urinary tract infection, pneumonia, skin and soft-tissue infection, gastroenteritis and pharyngitis are likely causes of sepsis other than the genital tract. Rarer causes include bacterial meningitis.

6.1 Mastitis

Mastitis is easily overlooked clinically, but may lead to breast abscesses,[7–10] necrotising fasciitis[1,10] and toxic shock syndrome.[1,10] During 2005–2008, two women died of mastitis-related sepsis, one with necrotising mastitis attributable to GAS and the other with *S.aureus*.[1] Outbreaks of PVL-producing MRSA in neonatal units have been associated with maternal carriage and vertical transmission during breastfeeding.[11,12] Immediate referral to hospital is indicated if the woman with mastitis is clinically unwell, if there is no response to oral antibiotics within 48 hours, if mastitis recurs or if there are very severe or unusual symptoms.[1]

6.2 Urinary tract infection

Gram-negative bacterial infections are particularly associated with the urinary tract. Acute pyelonephritis should be treated aggressively. Although not all women may warrant hospital admission, those with signs of sepsis, those who are unable to remain hydrated and those who are vomiting should be admitted.[13,14] The ESBL-producing coliforms are resistant to commonly used antimicrobials such as cephalosporins and co-amoxiclav and may necessitate usage of carbapenems or more unusual intravenous antimicrobials such as colistin.

Identification of urinary sepsis is primarily clinical but the presence of leucocytes, protein and blood in a mid-stream specimen of urine may be suggestive of current infection and a specimen should be sent for culture.

6.3 Pneumonia

Severe pneumonia should be managed in consultation with a respiratory physician and a medical microbiologist. A beta-lactam antibiotic together with a macrolide antibiotic is used to cover typical and atypical organisms.[15] Haemoptysis may be a feature of pneumococcal pneumonia. Severe haemoptysis and low peripheral white cell count suggest PVL-associated staphylococcal necrotising pneumonia, which has a mortality rate of more than 70% in young, fit people.[16]

Identification of the cause of pneumonia is by submitting a sample of sputum to the laboratory for culture. In some hospitals a urinary sample may be tested for pneumococcal antigen when sputum is not easily available.

6.4 Skin and soft-tissue infection

Any woman with suspected bacterial sepsis should be carefully examined for skin and soft-tissue infection, particularly looking at intravenous cannulae or injection sites and caesarean or episiotomy wounds. Swabs should be taken of any discharge. If drains, vascular access devices or other indwelling devices are suspected as the source of infection, they should be removed as soon as is practicable. The location of intravenous cannula sites should be recorded and inspected twice daily. Skin and soft-tissue infections are particularly associated with toxic shock syndromes.[5,10,17–20] Recurrent abscess formation, including labial abscesses, is a feature of PVL-producing staphylococci.[21]

Septicaemic seeding of streptococci from a uterine focus may give rise to a secondary focus in a limb, simulating a venous thrombosis.[1,20] Early necrotising fasciitis occurs deep in the tissues; therefore, in early necrotising fasciitis there may be no visible skin changes. As the necrotising process ascends to the skin, late infection produces blisters and obvious necrosis. The cardinal feature of necrotising fasciitis is of agonising pain, typically necessitating increasing amounts of strong analgesia culminating in use of opiates.[20]

Women with suspected thrombosis who are systemically unwell with any features of sepsis should be examined very carefully. Presence of shock or other organ dysfunction mandates rapid referral to critical care.

6.5 Gastroenteritis

Salmonella and *Campylobacter* rarely cause severe systemic infection and should be managed symptomatically unless features of bacteraemia are present. Diarrhoea and vomiting may be features of toxic shock syndrome[4,5,10,17–19] together with features of profound sepsis. *C. difficile* is rare but increasingly found in obstetric patients.[22]

6.6 Pharyngitis

Most cases of pharyngitis are viral, but approximately 10% of cases in adults are attributable to GAS. If three of the four Centor criteria[23] (fever, tonsillar exudate, no cough, tender anterior cervical lymphadenopathy) are present, treatment with an antibiotic is appropriate.

6.7 Infection related to regional anaesthesia

Spinal abscess is a very rare complication after regional anaesthesia in obstetric patients.[24,25] The usual organism responsible is *S. aureus*, with streptococci, Gram-negative rods and sterile specimens accounting for 15% each.[25] It is vital to consider the diagnosis, investigate and treat in a timely manner as permanent spinal cord or cauda equina damage may result if neural compression is prolonged.

7. What should prompt recognition of sepsis in the puerperium?

All health 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 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.

Mastitis must never be overlooked. ✓

Abdominal pain, fever (greater than 38°C) and tachycardia (greater than 90 beats/minute in the puerperium) are indications for intravenous antibiotics and senior clinical review. ✓

Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided for pain relief in cases of sepsis as they impede the ability of polymorphs to fight GAS infection. ✓

Sepsis should be considered in all recently delivered women who feel unwell and have pyrexia or hypothermia.[1]

The common symptoms of sepsis in the puerperium include fever, diarrhoea, vomiting, abdominal pain, generalised maculopapular rash (staphylococcal or streptococcal sepsis), offensive vaginal discharge and signs of infection in caesarean wounds.[1,2] Evidence level 3

Agonising pain out of proportion to the clinical signs suggests a deep infection, and necrotising fasciitis/myositis must be considered.[9,17,18,20]

Evidence level 3

Table 2 details common symptoms of sepsis in the puerperium.

A pain scoring system is useful in charting progress. Since NSAIDs significantly impede the ability of polymorphs to fight infection caused by GAS, they should be avoided for pain relief in cases of sepsis.[20,26]

Table 2. Common symptoms of sepsis in the puerperium[1,2]

Fever, rigors (persistent spiking temperature suggests abscess). Beware: normal temperature may be attributable to antipyretics or NSAIDs
Diarrhoea or vomiting – may indicate exotoxin production (early toxic shock)
Breast engorgement / redness
Rash (generalised maculopapular rash)
Abdominal / pelvic pain and tenderness
Wound infection – spreading cellulitis or discharge
Offensive vaginal discharge (smelly: suggestive of anaerobes; serosanguinous: suggestive of streptococcal infection)
Productive cough
Urinary symptoms
Delay in uterine involution, heavy lochia
General – non-specific signs such as lethargy, reduced appetite.

Some cases of sepsis in the puerperium may present initially only with severe abdominal pain, in the absence of fever and tachycardia.[18,19]

Any widespread rash should suggest early toxic shock syndrome, especially if conjunctival hyperaemia or suffusion is present.[5,9,17–19] A generalised macular rash is present in most cases of staphylococcal toxic shock syndrome but in only 10% of cases of streptococcal toxic shock syndrome. Conjunctival suffusion is a classic sign of toxic shock syndrome.[9,18,26] See Appendix 1 for a definition and classification of toxic shock syndrome.

8. What is the optimum way to monitor women with suspected sepsis in the puerperium?

Monitoring of the woman with suspected severe sepsis or established sepsis should be multidisciplinary but preferably under the leadership of a single consultant. A senior obstetrician should be involved, in consultation with an intensivist, microbiologist or infectious disease clinician. ✓

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. ✓

While MEOWS charts have become widespread since the recommendations of the CEMACH[2] report, unfortunately there is no standardisation. (An example from the Obstetric Anaesthetists' Association is available.[27]) Swanton et al. have developed a MEOWS chart taking into account the variations in charts used by individual hospitals.[28] Abnormal scores should not just be recorded but should also trigger an appropriate response.[1]

All women who are unwell during the puerperium require regular and frequent observation. Handover arrangements should be robust. Regular contact with family members is required.

9. What infectious disease history/information should be noted?

Any recent illness or exposure to illness in close contacts, particularly streptococcal infections, should be noted. ✓

A history of recent sore throat or prolonged (household) contact with family members with known streptococcal infections (pharyngitis, impetigo, cellulitis) has been implicated in cases of GAS sepsis.[1,17,18] In the CMACE report, five of six women with GAS admitted to hospital with septic shock had a history of recent sore throat or respiratory infection.[1]

Intravenous drug misuse carries a high risk of staphylococcal and streptococcal sepsis as well as generalised immunosuppression of chronic disease, endocarditis and blood-borne viruses.[1]

Recent febrile illnesses, especially if associated with chills and rigors, suggest bacteraemia.

Gastrointestinal symptoms such as diarrhoea and vomiting may be attributable to food-borne pathogens, *C. difficile* infection or early toxic shock.[10,19,20]

Prior carriage of or infection with multiresistant organisms such as ESBL-producing Gram-negative bacteria, vancomycin-resistant enterococci and MRSA should be noted on admission as empirical antimicrobial choice will be affected in the event of sepsis. Appropriate infection control precautions may need to be instituted.

Any inter-current illness warranting antimicrobials should be noted on admission.

Ingestion of unpasteurised milk products raises the possibility of infection with *Salmonella*, *Campylobacter* or *Listeria*. *Chlamydophila psittaci* is acquired by contact with aborting sheep or infected birds or by cross-infection from washing contaminated clothing. Q fever is caused by *Coxiella burnetii* after inhalation of infectious particles from birthing animals or contaminated dust.

Recent foreign travel or hospitalisation abroad is associated with a high carriage rate of multiresistant organisms and hence should prompt discussions with a microbiologist to ensure isolation procedures and diagnostic tests are appropriate.

10. What are the appropriate triggers or features of sepsis in the puerperium that should prompt hospital admission?

Community carers should be aware of the importance of early referral to hospital of recently delivered women who feel unwell and have pyrexia, and should be aware of the possibility of sepsis in the puerperium (see Table 2). ✓

If sepsis is suspected in the community, urgent referral to hospital is indicated. ✓

'Red flag' signs and symptoms (see below) should prompt urgent referral for hospital assessment and, if the woman appears seriously unwell, by emergency ambulance:

- pyrexia more than 38°C
- sustained tachycardia more than 90 beats/minute
- breathlessness (respiratory rate more than 20 breaths/minute; a serious symptom)
- abdominal or chest pain
- diarrhoea and/or vomiting
- uterine or renal angle pain and tenderness
- woman is generally unwell or seems unduly anxious or distressed.[1]

Early presentation of sepsis (less than 12 hours post-birth) is more likely to be caused by streptococcal infection, particularly GAS, and severe continuous pain suggests necrotising fasciitis.[1,10,20]

Infection must also be suspected and actively ruled out when a recently delivered woman has persistent vaginal bleeding and abdominal pain. If there is any concern, the woman must be referred back to the maternity unit as soon as possible.[1]

The speed of onset or deterioration in symptoms and signs is important. Early treatment with antibiotics, whether oral or parenteral, may be crucial in determining the outcome. Abdominal pain, fever (greater than 38°C) and tachycardia (greater than 90 beats/minute) are indications for admission for intravenous antibiotics.[1]

In hospital, high-dose intravenous broad-spectrum antibiotics should be started immediately, without waiting for the results of investigations, because once infection becomes systemic the woman's condition can deteriorate extremely rapidly, with death ensuing within a few hours if untreated.[1]

11. What are the appropriate triggers for involvement of other specialties?

All cases of sepsis in the puerperium should be discussed with a clinical microbiologist or infectious diseases physician. Appropriate specimens should be sent for urgent examination. Antimicrobials should be started within 1 hour of recognition of severe sepsis. ✓

Women with previously documented carriage of or infection with multiresistant organisms (e.g. ESBL-producing organisms, MRSA, GAS or PVL-producing staphylococci) should prompt notification of the infection control team. ✓

Suspicion of necrotising fasciitis should prompt involvement of intensive care physicians and referral for surgical opinion, ideally from plastic and reconstructive surgeons if available.[22] ✓

It is important that the expertise of other specialist teams is sought early in cases of suspected sepsis in the puerperium. There may be a need to consider infections less commonly seen, and appropriate advice needs to be sought as early as possible to expedite the appropriate investigations or management.

12. What investigations should be performed?

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 6 hours of the suspicion of severe sepsis to guide management. Serum lactate ≥ 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. This could include a chest X-ray, pelvic ultrasound scan or computed tomography scan if pelvic abscess is suspected. D

Other samples taken should be guided by the clinical suspicion of focus of infection as appropriate. ✓

Routine blood tests should include full blood count, urea, electrolytes and C-reactive protein (CRP). ✓

Any woman with symptoms of tonsillitis/pharyngitis should have a throat swab sent for culture. ✓

If the MRSA status of the woman is unknown, a premoistened nose swab may be sent for rapid MRSA screening where such testing is available. ✓

Blood cultures and other samples taken should be guided by clinical suspicion of focus of infection, such as throat swabs, mid-stream urine, high vaginal swab, throat swab, placental swabs, sputum, cerebrospinal fluid, epidural site swab, caesarean section or episiotomy site wound swabs and expressed breast milk, and should ideally be obtained prior to starting antibiotic therapy as the results may become uninformative within a few hours of commencing antibiotics. Antibiotics should be given as soon as possible. Results of laboratory tests should be checked and recorded regularly and the medical microbiologist consulted to ensure specimens are processed appropriately and results communicated directly to the clinician at the earliest opportunity. Gram stain, culture results and sensitivities should be used to tailor antimicrobial therapy.

If diarrhoea is particularly offensive following antimicrobial therapy, a stool sample should be submitted for *C. difficile* toxin testing.[22] A history of diarrhoea warrants routine culture (e.g. *Salmonella*, *Campylobacter*). The laboratory should be informed if there is a clinical indication for investigations for unusual pathogens such as *Listeria monocytogenes* (consumption of soft cheese or cured meats) or if there is a history of foreign travel (parasites, typhoid or cholera).

Bacterial numbers may be scanty or not seen on initial Gram staining of swabs, fluids or debrided tissue. However, organisms seen on Gram staining will guide empirical prescribing. A paucity of leucocytes and the presence of Gram-positive cocci in chains indicate streptococcal infection. 'Mixed organisms' (i.e. mixed Gram- negative and -positive organisms) would suggest the possibility of gut organisms, including anaerobes, as part of a synergistic infection.

Diagnostic criteria for sepsis are available in Appendix 2 (in the absence of specific criteria for women in the puerperium).

Thrombocytosis (high platelet count) with a rising CRP and a swinging pyrexia usually indicates a collection of pus or an infected haematoma in the woman.

Table 3 indicates tasks which should be performed within the first 6 hours of the identification of severe sepsis.

Table 3. Tasks to be performed within the first 6 hours of the identification of severe sepsis; modified from the Surviving Sepsis Campaign Resuscitation Bundles[3]

Obtain blood cultures prior to antibiotic administration
Administer broad-spectrum antibiotic within 1 hour of recognition of severe sepsis
Measure serum lactate
In the event of hypotension and/or a serum lactate greater than 4 mmol/l: Deliver an initial minimum 20 ml/kg of crystalloid or an equivalent Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure above 65 mmHg
In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or serum lactate greater than 4 mmol/l: Achieve a central venous pressure of ≥ 8 mmHg Achieve a central venous oxygen saturation ≥ 70% or mixed venous oxygen saturation ≥ 65%

13. How should sepsis in the puerperium be managed?

The focus of infection should be sought and dealt with. This may be by uterine evacuation or by drainage of a breast, wound or pelvic abscess. Broad-spectrum antibiotics should be given to cover these procedures. ✓

13.1 Which antibiotics should be used?

Administration of intravenous broad-spectrum antibiotics within 1 hour of suspicion of severe sepsis, with or without septic shock, is recommended as part of the Surviving Sepsis resuscitation care bundle. D

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

A combination of either piperacillin/tazobactam or a carbapenem plus clindamycin provides one of the broadest ranges of treatment for severe sepsis. ✓

MRSA may be resistant to clindamycin, hence if the woman is or is highly likely to be MRSA-positive, a glycopeptide such as vancomycin or teicoplanin may be added until sensitivity is known. ✓

Breastfeeding limits the use of some antimicrobials, hence the advice of a consultant microbiologist should be sought at an early stage. ✓

Antibiotic therapy should be guided by the Gram stain of any aspirate or biopsy; however, in practice the patient is usually so sick there is no time to wait, hence initial empirical prescribing of broad-spectrum antibiotics is essential. Intravenous broad-spectrum antibiotics should be given within 1 hour of suspicion of severe sepsis.[3] Evidence level 4

Clindamycin is not nephrotoxic and switches off the production of superantigens and other exotoxins.[18,20,29] Therefore, together with either piperacillin/tazobactam or a carbapenem, clindamycin provides broad cover in severe sepsis.

Evidence level 4

The 2003–2005 CEMACH report[2] referred to the use of cefuroxime and metronidazole for sepsis in the puerperium. However, cefuroxime is no longer part of many hospital formularies because of the association with *C. difficile*. Neither agent provides any protection against MRSA, *Pseudomonas* or ESBL (see Appendix 3).

In ESBL infection, piperacillin/tazobactam is likely to be ineffective.

Information on antimicrobials which may aid in guiding choice is given in Table 4, but hospital guidelines differ and local guidance should be followed since the incidence of resistant organisms varies throughout the UK.The decision as to which antimicrobials to include in the hospital formulary and maternity unit guidelines for severe sepsis in the puerperium should be agreed by clinicians and the hospital microbiologist.

National guidelines for the management of community-acquired pneumonia,[30] PVL-producing *S. aureus*[31] and MRSA-associated infections[32,33] should be consulted where necessary.

Evidence level 4

Table 4. Antimicrobial choices and limitations of antimicrobials

Antimicrobial	Limitations
Co-amoxiclav	Does not cover MRSA, Pseudomonas or ESBL-producing organisms
Metronidazole	Only covers anaerobes
Clindamycin	Covers most streptococci and staphylococci, including many MRSA, and switches off exotoxin production with significantly decreased mortality[18,29,34] Not renally excreted or nephrotoxic
Piperacillin/tazobactam and carbapenems	Covers most organisms except MRSA and are renal sparing (in contrast to aminoglycosides) Piperacillin/tazobactam does not cover ESBL producers
Gentamicin (as a single dose of 3–5 mg/kg)	Poses no problem in normal renal function but if doses are to be given regularly serum levels must be monitored[35]

13.2 What are some of the adverse effects of treatment?

Treatment with any antimicrobial can cause allergic reactions, including skin rashes. However, it should be remembered that, particularly in toxic shock, a maculopapular or blanching erythema may be exotoxin related and not an allergy to the therapy.

Diarrhoea, particularly if offensive or developing after any antimicrobial therapy, should be sent for *C. difficile* toxin testing. The organism does not infect neonates but can cause up to 30% mortality in mothers if untreated.[22] Pending the result of testing, oral metronidazole or oral vancomycin are used empirically where clinically justified.

13.3 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 immunodulatory effect and in staphylococcal and streptococcal sepsis also neutralises the super-antigen effect of exotoxins and inhibits production of tumour necrosis factor and interleukins.

High-dose IVIG has been used in pregnant and postpartum women[36–39] and is effective in exotoxic shock (i.e. toxic shock attributable to streptococci and staphylococci),[40–44] but there is little evidence of benefit in Gram-negative (endotoxin-related) sepsis. The main contraindication to IVIG use is a congenital deficiency of immunoglobulin A.[46]

Evidence level 3

There are now many case reports[36–43] and some small series[44,46] where dramatic improvement resulted after administration of IVIG.

IVIG is available from the blood transfusion department. 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 guidelines/protocols for replacement therapy in haematology patients may be used. However, when faster replacement is necessary in severely ill patients, the Mount Sinai hospital protocol may be helpful.[47]

Evidence level 4

13.4 Where should women with sepsis be cared for?

Women with sepsis in the puerperium are best managed in a hospital where diagnostic services are easy to access and intensive care facilities are readily available. ✓

Early referral to hospital may be life saving. ✓

Sepsis in the puerperium may have an insidious onset but then a fulminating course. Early discharge from the delivery unit means that some women will develop infection after they return home, or they may have given birth at home.

The CEMACH 2002–2005 report noted that some women who died were managed in 'units ill equipped to deal with them'.[2]

13.5 What are the indications for admission to the intensive care unit (ICU)?

The presence of shock or other organ dysfunction in the woman is an indication for admission to the ICU. ✓

The diagnosis of sepsis should trigger discussion with the critical care team. Features of severe sepsis which are likely to require admission to the ICU are shown in Table 5.

Table 5. Indications for admission of the woman to the ICU;[3] adapted from Plaat and Wray, 2008[48]

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	Multiorgan failure Uncorrected acidosis Hypothermia

The treatment of hypotension and oliguria in non-pregnant septic patients involves aggressive fluid replacement. However, postpartum women may be more susceptible to the development of pulmonary oedema than non-pregnant patients after circulatory fluid overload. Achieving the correct balance between these potentially conflicting aims is exceedingly difficult, and central venous pressure monitoring and

vasopressor treatment are likely to be required on the ICU. It is important to involve the anaesthetic and critical care teams early to advise on early management and subsequent transfer.

13.6 How should a drug-misusing woman be managed?

Women with a history of substance misuse are usually monitored under multiagency care. The local drugs advisory specialist team and existing hospital guidelines for care of substance misusers /drug users should be consulted. ✓

Any injection-site lesions should be swabbed and an MRSA screen performed. ✓

A history of intravenous drug use and features of sepsis of unknown site requires a search for bacterial endocarditis or abscesses spread via the bloodstream. Current or former intravenous drug users usually have very difficult vascular access. Alternative access devices such as a central venous catheter or peripherally inserted central catheter are more likely to be required for long-term intravenous antibiotic treatment, and early referral of the woman to a vascular access team or equivalent is desirable.

Effects on breastfeeding and other practical management issues necessitate the involvement of neonatologists and the local specialist drugs team.

14. What are the infection control issues?

The woman should be isolated in a single room with en suite facilities to reduce the risk of transmission of infection. ✓

Healthcare workers (defined as doctors, midwives, nurses, anaesthetists and members of the wound care team) should wear personal protective equipment including disposable gloves and aprons when in contact with the woman, equipment and their immediate surroundings. ✓

Breaks in the skin of the woman or carer must be covered with a waterproof dressing. ✓

Fluid-repellent surgical masks with visors must be used at operative debridement /change of dressings of GAS necrotising fasciitis and for other procedures where droplet spread is possible. ✓

Visitors should be offered suitable information and relevant personal protective equipment while the woman is isolated. ✓

Mothers or neonates infected or colonised with high-risk organisms such as GAS, MRSA or PVL-producing staphylococci may generate outbreaks within the healthcare setting, especially for other babies in nursery units and staff.[49–51] The local infection control team should be informed of any such cases and appropriate isolation precautions followed. Healthcare workers should wear personal protective equipment including disposable gloves and aprons when in contact with the woman, equipment and their immediate surroundings.[49,52]

Isolation in a single room with en suite facilities is recommended since numerous streptococcal outbreaks have occurred in maternity units, some involving shared toilet and shower facilities.[51]

MRSA and GAS are easily transmitted via the hands of healthcare workers and via close contact in households.[49] Local infection control guidelines should be followed for hospital-specific isolation and contact precautions. PVL-associated infections should be managed in accordance with national guidelines.[32,52]

Non-maternity isolations of GAS – for example, when known about before the patient is admitted, or diagnosed in a healthcare worker – should be reported to the infection control team/director of infection prevention and

control/occupational health, as appropriate. Strict infection control precautions should be applied, both to delivery procedures and during the hospital stay.[49,52]

15. What are the neonatal issues if sepsis develops in the puerperium?

The baby is especially at risk of streptococcal and staphylococcal infection during birth and during breastfeeding. The umbilical area should be examined and a paediatrician consulted in the event of sepsis in the puerperium. D

If either the mother or the baby is infected with invasive GAS in the postpartum period, both should be treated with antibiotics. ✓

GAS and PVL-producing *S. aureus* infections have been transmitted to babies during breastfeeding, causing severe infection.[11] GAS poses the highest risk of sepsis in the neonate, with numerous cases where both mother and baby have been affected.[49] Hence, antimicrobial prophylaxis should be given routinely to neonates of mothers with GAS infection.[52]

The infant of a mother colonised with Group B Streptococci should be managed as per RCOG Green-top Guideline No.36: *Prevention of early onset neonatal group B streptococcal disease*.[53]

Evidence level 4

16. What are the indications for prophylaxis to family/staff?

Close household contacts should be warned about the symptoms of GAS infection and told to seek medical attention should symptoms develop. Asymptomatic contacts may warrant prophylaxis. ✓

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

Only the meningococcus (Neisseria meningitidis) and GAS merit consideration of prophylaxis for family or staff.

MRSA and PVL-producing *S. aureus* are transmitted during breastfeeding and close contact. Although routine prophylaxis is not indicated, the neonate should be observed closely and liaison with the infection control team is advised.

The Health Protection Agency has produced detailed guidelines for investigation, control and prevention of spread of GAS infection in healthcare settings in the UK.[52] Generally, prophylaxis for GAS organisms would be administered in the event of close contact (kissing or household contacts) and for healthcare workers with exposure to respiratory secretions (e.g. suctioning).[49]

Evidence level 4

17. Can sepsis in the puerperium be prevented or detected earlier?

All pregnant and recently delivered women should be informed of the signs and symptoms of genital tract infection and how to prevent its transmission. ✓

Any GAS identified during pregnancy should be treated aggressively. ✓

All pregnant and recently delivered women need to be informed of the signs and symptoms of genital tract infection and how to prevent its transmission. Advice to all women should include verbal and written information about its prevention, signs and symptoms and the need to seek advice early if concerned, as well as the importance of good personal hygiene. This includes avoiding contamination of the perineum by washing hands before and after using the lavatory or changing sanitary towels. It is especially necessary when the woman or her family or close contacts have a sore throat or upper respiratory tract infection. [1]

All clinical staff must undertake regular, written, documented and audited training for the identification and initial management of serious obstetric conditions or emerging potential emergencies, such as sepsis, which need to be distinguished from commonplace symptoms in pregnancy.[1]

Any GAS identified during pregnancy should be treated aggressively. Several cases of women with known GAS infection have been reported where GAS was not treated, resulting in maternal death.[1]

Any signs of infection or necessity to administer antibiotics noted during a woman's hospital stay should be reported directly to her community carers (GP, midwives and health visitors) when she is discharged so that appropriate follow-up visits may be arranged and the significance of developing symptoms recognised.

18. Suggested audit topics

- Number of women admitted to hospital within 6 weeks of delivery for sepsis.
- Number of postpartum women admitted to the ICU with sepsis as the primary diagnosis.
- Rate of hospital-acquired infection in the maternity unit.
- Rate of wound infection after caesarean section.
- Number of women with specific infections: MRSA, GAS, *Clostridia sepsis*.
- Percentage of women who had antibiotic therapy started within 1 hour of recognition of bacterial sepsis after pregnancy. Target: 100% within 1 hour.[1]

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APPENDIX 1

Staphylococcal and streptococcal toxic shock syndrome: clinical disease definition.

Staphylococcal toxic shock syndrome (TSS)[17]	Streptococcal toxic shock syndrome (STSS)[17,26]
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 (adults)	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: ● gastrointestinal: 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 ● hepatic: total bilirubin 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 >176µmol/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

APPENDIX 2

Diagnostic criteria for sepsis modified from Levy et al.,[54] using CMACE[1] and Lewis[2] where pregnancy-specific parameters available.

Infection, documented or suspected, and some of the following:
General variables:
Fever (> 38ºC)
Hypothermia (core temperature < 36ºC)
Tachycardia (> 90 beats/minute)
Tachypnoea (> 20 breaths/minute)
Impaired mental state, altered conscious level
Considerable oedema or positive fluid balance (> 20ml/kg over 24 hours)
Hyperglycaemia in the absence of diabetes (plasma glucose > 7.7 mmol/l)
Bruising or discoloration of skin suggests **late** fasciitis (often pain receding as cutaneous anaesthesia supervenes as nerves die)
Inflammatory variables:
White blood cell (WBC) count > 12 x 10^9l
Leucopenia (WBC count < 4 x 10^9l)
Normal WBC count with > 10% immature forms
Plasma C-reactive protein > 7mg/l (usually significantly higher in bacterial sepsis)
Haemodynamic variables:
Arterial hypotension (systolic blood pressure < 90mmHg; mean arterial pressure < 70mmHg; or systolic blood pressure decrease > 40mmHg)
Tissue perfusion variables:
Raised serum lactate ≥ 4 mmol/l
Decreased capillary refill or mottling
Organ dysfunction variables:
Arterial hypoxaemia (PaO_2 (partial pressure of oxygen in arterial blood) /FIO_2 (fraction of inspired oxygen) < 40kPa); **sepsis is severe if < 33.3kPa in the absence of pneumonia or < 26.7kPa in the presence of pneumonia**
Oliguria (urine output < 0.5ml/kg/hr for at least two hours, despite adequate fluid resuscitation)
Creatinine rise of > 44.2µmol/l; **sepsis is severe if creatinine level** > 176µ**mol/l**
Coagulation abnormalities (International Normalised Ratio [INR] > 1.5 or activated partial thromboplastin time [APTT] > 60 seconds)
Thrombocytopaenia (platelet count < 100 x10^9/l)
Hyperbilirubinaemia (plasma total bilirubin > 70µmol/l)
Ileus (absent bowel sounds)

APPENDIX 3

Suggested empirical antimicrobials for use in bacterial sepsis after pregnancy.

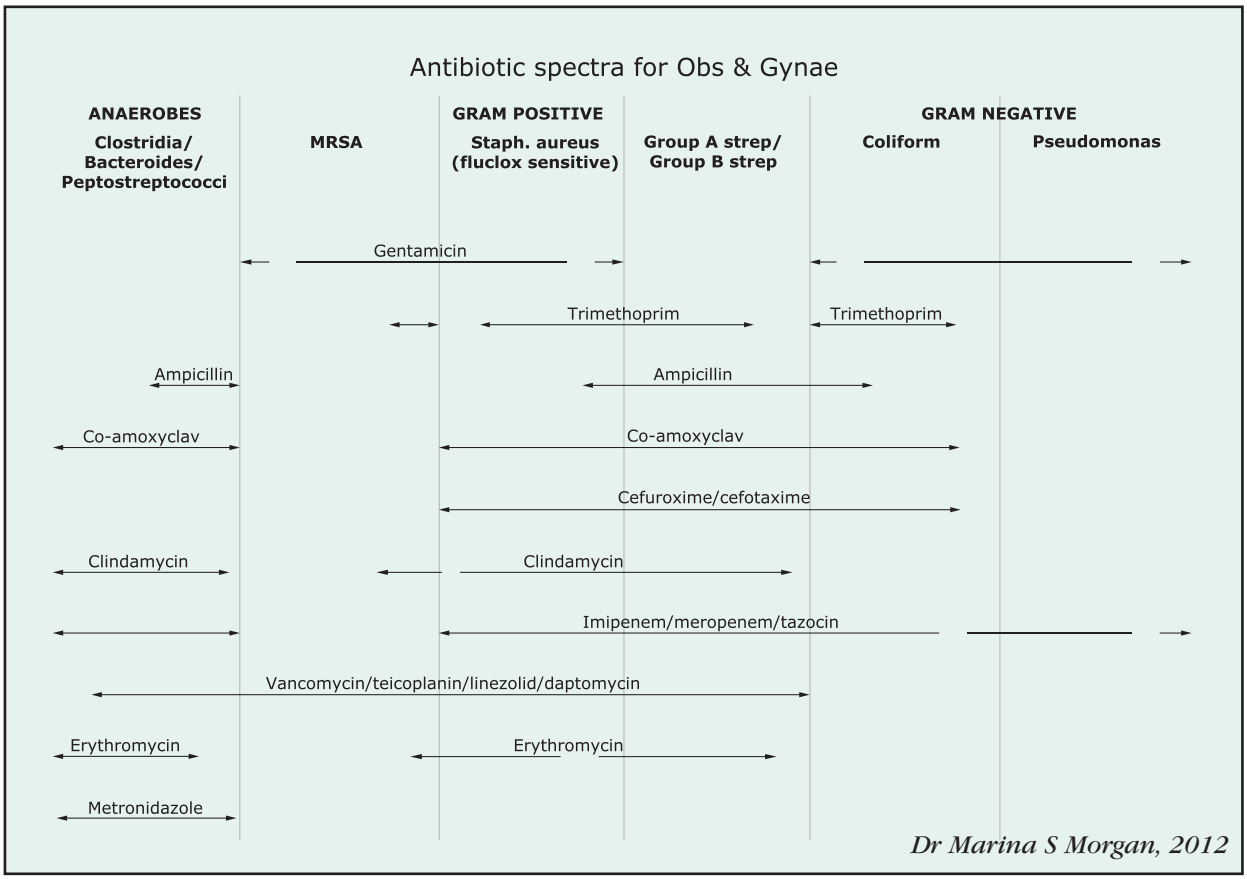
Condition	Organisms	Antimicrobial	If allergic	Notes
Mastitis	MSSA Streptococci	Flucloxacillin + clindamycin	Vancomycin + clindamycin	Trough level vancomycin 5–20 mg/l necessary
Mastitis	MRSA Streptococci	Vancomycin + clindamycin	Clindamycin/teicoplanin are alternatives	
Caesarean section wound infection or intravenous cannula site infection	MRSA Streptococci	Vancomycin + clindamycin	Clindamycin/teicoplanin are alternatives	
Caesarean section wound infection or intravenous cannula site infection	MSSA Streptococci	Flucloxacillin + clindamycin	Vancomycin + clindamycin	
Endometritis	Gram-negative anaerobes Streptococci	Gentamicin **one dose** immediately + cefotaxime + metronidazole	Gentamicin + clindamycin + ciprofloxacin	
Acute pyelonephritis	Gram-negative bacteria Occasionally staphylococci and streptococci	Cefotaxime + gentamicin (gentamicin administered once only)	Gentamicin + ciprofloxacin	ESBLs: gentamicin + meropenem
Toxic shock syndrome	Staphylococci Streptococci	Flucloxacillin + clindamycin + gentamicin (gentamicin administered once only) For MRSA use vancomycin instead of flucloxacillin	Vancomycin + clindamycin + immediately gentamicin (gentamicin administered once only) **or** Linezolid + gentamicin (gentamicin administered once only)	Regimen **must** contain an antitoxin agent such as clindamycin[28] or linezolid Consider IVIG[44]
Severe sepsis, no focus	MRSA, streptococci, Gram-negatives (including ESBL producers + *Pseudomonas*) and anaerobes	Meropenem + clindamycin + gentamicin (gentamicin usually administered once only)	Clindamycin + gentamicin + metronidazole + ciprofloxacin	In those with severe penicillin allergy, carbapenems are contraindicated

ESBL = extended-spectrum beta-lactamase; IVIG = intravenous immunoglobulin; MRSA = meticillin-resistant *Staphylococcus aureus*; MSSA = meticillin-sensitive *Staphylococcus aureus*.

Note: these are suggestions, and local guidelines should be consulted since policies and sensitivities differ between hospitals. All complex cases or unusual allergies should be discussed with a microbiologist and therapy should be rationalised as soon as possible.

APPENDIX 4

Antibiotic spectra for obstetrics and gynaecology.



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

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APPENDIX 5

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

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1–	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
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
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

Grades of recommendations

A	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
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+
C	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++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Good practice point

✓	Recommended best practice based on the clinical experience of the guideline development group

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Conflicts of interest; none declared

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.

