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REVIEW ARTICLE

# Sepsis in obstetrics and the role of the anaesthetist

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**ABSTRACT**
Sepsis in pregnancy and the puerperium remains a significant cause of maternal mortality and morbidity worldwide. Major morbidity arising as a result of obstetric sepsis includes fetal demise, organ failure, chronic pelvic inflammatory disease, chronic pelvic pain, bilateral tubal occlusion and infertility. Early recognition and timely response are key to ensuring good outcome. This review examines the clinical problem of sepsis in obstetrics and the role of the anaesthetist in the management of this condition.


***Keywords***: Sepsis; Obstetrics; Morbidity; Mortality

## Introduction

In the most recent Confidential Enquiries into Maternal Deaths in the UK, sepsis was the leading cause of direct maternal death, and the maternal mortality rate from sepsis has almost tripled in the last 25 years.[1] Worldwide, sepsis accounts for 15% of maternal deaths.[2] The Scottish Confidential Audit of Severe Maternal Morbidity showed a rate of septicaemic shock of 0.11 per 1000 maternities in the 2006–2008 triennium.[3] In a retrospective analysis of 'near-miss cases' from a tertiary maternity unit in the United States, sepsis was responsible for 15% of cases.[4] Sepsis in the obstetric population poses significant challenges: the physiological changes of pregnancy may mask the clinical signs of sepsis and when it occurs in the antenatal period maternal deterioration can quickly lead to fetal compromise. Early recognition and diagnosis with rapidly instituted therapy are key to ensuring a good outcome.

## History

During the 18th, 19th and 20th centuries, sepsis was the leading cause of maternal death in England and Wales. Between the years 1847 and 1903 there were 93 342 recorded maternal deaths from puerperal fever.[5,6] Accuracy of record keeping improved after puerperal fever became a notifiable disease in 1899 and it remained so until the late 1960s. It was long recognised that puerperal fever occurred in epidemics in 'lying-in' (maternity) hospitals. In 1867 Florence Nightingale was forced to close the lying-in ward she had established at King's College Hospital only five years previously, because of excessive rates of puerperal fever.

The earliest recognition that puerperal fever was contagious came from Alexander Gordon's *Treatise on the Epidemic of Puerperal Fever in Aberdeen* published in 1795.[7] In America this observation was later supported by Oliver Wendell Holmes' 1843 paper *The Contagiousness of Puerperal Fever*.[8] A significant contribution was made by Ignaz Semmelweis working at the Vienna Maternity Hospital. He recognised that medical students who were attending post-mortems, and then labouring women, were transmitting infection. In 1847 he introduced hand washing using disinfectant, after which there was a dramatic fall in the incidence of puerperal fever from 18% to 1.27%.[9,10]

In the early part of the last century in the UK there was growing concern at the number of women who died in association with childbirth. A government-commissioned investigation into maternal deaths in England published in 1937, found that sepsis accounted for 39% of all deaths.[11] In 1935 Leonard Colebrook, a physician working at Queen Charlotte's Hospital in London, gave the first sulphonamide, Prontosil, to a woman who was severely ill with puerperal sepsis and she made a full recovery.[5] This event heralded the introduction of antibiotics in the treatment of puerperal sepsis, and by the mid-1940s penicillin had become commercially available. Thus by the time of the first formal confidential enquiry report into maternal death, published in 1957, maternal deaths from sepsis had already started to decline sharply (Fig. 1).[12] Over the following decades this decline was associated with other causes of maternal death coming to the fore in the developed world. However, in the UK sepsis has recently ta-

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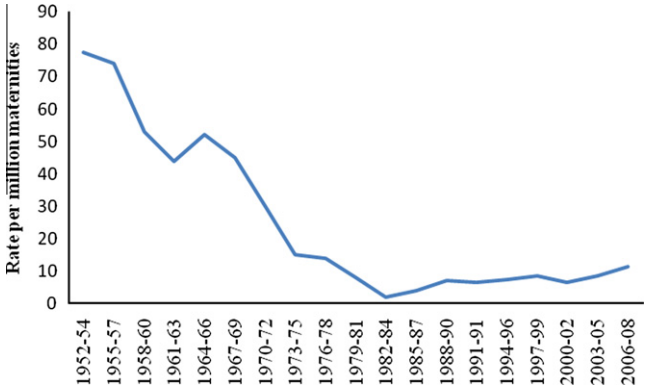


**Fig. 1** Trends in maternal mortality from genital tract sepsis; England & Wales 1952–1984, UK 1985–2008.

ken over from thromboembolic disease and is once again the leading cause of maternal death.[1] In the developing world there is significant regional variation in many of the leading causes of maternal death. In Africa, haemorrhage is the leading cause of death, whereas in Latin America it is hypertensive disease. In contrast, deaths from sepsis do not show this variation and are consistently a significant cause of maternal mortality in all parts of the developing world.[13]

## Definitions

The term sepsis includes illness that ranges from minor signs and symptoms through to organ dysfunction and shock. There is currently no universally accepted definition of sepsis in obstetric practice. The term puerperal sepsis is still used to describe sepsis occurring after delivery and the World Health Organisation (WHO) 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.[14]

A widely used definition for sepsis in the non-pregnant patient has come from the American College of Chest Physicians and the Society of Critical Care Medicine (Table 1).[15] This was modified in 2001 by the International Sepsis Definition Forum to include alterations in physiological variables, in order to convey more accurately the clinical experience. However, because of the physiological changes of pregnancy and particularly those around the time of delivery, this definition lacks validity in obstetric patients.

There are various other reasons that add to the difficulty of defining sepsis in obstetric practice. Sepsis may arise in an obstetric patient at any time: before delivery, during labour or in the postnatal period. In addition, sepsis in obstetric patients can arise from many sources and is not limited to infections arising from the genital tract. This difficulty in reaching a definition is demonstrated by the organisation of cases in the UK Confidential Enquiry Reports. Deaths due to Group A beta-haemolytic Streptococcus pyogenes, as well as other infections related to pregnancy or delivery, are classified as direct deaths, whereas deaths from infections unrelated to the genital tract such as pneumococcal meningitis and human immunodeficiency virus (HIV) are

**Table 1 American College of Chest Physicians and Society of Critical Care Medicine definitions related to sepsis**

***Systemic inflammatory response syndrome***

Systemic inflammatory response syndrome (SIRS) is a widespread inflammatory response to a variety of severe clinical insults. This syndrome is clinically recognized by the presence of two or more of the following:

- Temperature >38°C or <36°C
- Heart rate >90 beats/min
- Respiratory rate >20 breaths/min or $PaCO_2 < 32$ mmHg
- White blood cells $>12 \times 10^9$/dL or $<4 \times 10^9$/dL or >10% immature (band) forms

***Sepsis***

Sepsis is the systemic response to infection. Thus in sepsis, clinical signs describing SIRS are present together with definitive evidence of infection

***Severe sepsis***

Sepsis is considered severe when associated with organ dysfunction, hypoperfusion or hypotension. Manifestations of hypoperfusion may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status

***Septic shock***

Septic shock is sepsis with hypotension despite adequate fluid resuscitation. It includes perfusion abnormalities such as lactic acidosis, oliguria, or an acute alteration in mental status. Patients receiving inotropic or vasopressor agents may not necessarily be hypotensive at the time that perfusion abnormalities are present

classified as indirect maternal deaths. A new pathological classification has been proposed for future confidential enquiries.[1]

The WHO Technical Working Group has introduced the term puerperal infections as a more general term than puerperal sepsis, to include not only infections related to genital tract sepsis, but also all extra-genital infections and incidental infections (Table 2).

## The immune system in pregnancy

Pregnancy has traditionally been viewed as an immunocompromised state arising as a result of the necessity not to reject the fetus immunologically, and therefore placing the mother at increased risk of infectious diseases. However, there is now a wealth of evidence to suggest that rather than being a immunosuppressed state, pregnancy presents a modified immune state whereby there may be contrasting responses to different infections, responses that are also determined by the stage of pregnancy.[16,17] From a logical and evolutionary perspective a successful pregnancy is key to the conservation of the species and it has been suggested by Wilson that pregnancy is a ''paradoxical immune state where foreign tissue is not only tolerated but nurtured''.[18]

A competent immune response is essential to protect the mother directly and the fetus indirectly. The immune response depends on either cell-mediated immunity (particularly T lymphocytes) or the humoral response (antibodies secreted by B lymphocytes and plasma cells). During pregnancy progesterone and oestrogen reduce T cell proliferation and there is consequently a reduction in cell-mediated immunity which might otherwise prove harmful to the fetus. The maternal immune system is therefore biased towards humoral immunity.[19] Coupled with this is the developing active immune system of the fetus, which will also modify the maternal response to infection.

Three distinct immunological phases have been described in pregnancy, roughly corresponding with the first, second and third trimesters, and associated with dramatic changes in cytokine levels.[17] The combined effect of these interactions serves to explain why in pregnancy women may exhibit a diverse response to infection, depending not only on the infecting organism but also on the stage of the pregnancy, e.g. pregnant women living in malarial endemic areas are more susceptible to malarial infection in the first-half of pregnancy and this susceptibility decreases as the pregnancy progresses.[20]

**Table 2 World Health Organisation definition of puerperal infections**

| |
|---|
| Infections of the genitourinary system related to labour, delivery and the puerperium:<br>Infections related to the uterus and its associated structures (endometritis)<br>Infections related to the urinary tract |
| Infections specifically related to the birth process but not of the genitourinary system:<br>e.g. breast abscess |
| Incidental infections:<br>e.g. malaria, respiratory tract infections |

## Risk factors and causes of sepsis in obstetrics

Sepsis can arise at any time during pregnancy and the puerperium, and may develop as a result of bacteraemia (although bacteraemia does not always lead to sepsis), or as a result of local infection. Risk factors for maternal sepsis may be divided into intrinsic patient factors and obstetric factors (Table 3). In addition, women from poor socio-economic backgrounds are at greater risk of sepsis although the mechanisms are unclear.[21] Although none of the women who died from sepsis in the 2006–2008 UK Centre for Maternal and Child Enquiries (CMACE) report were obese, obesity remains a significant risk factor for obstetric sepsis; in the 2003–2005 report the majority of the women who died from sepsis were obese.[22]

In patients with sickle cell disease functional asplenia results in increased susceptibility to bacterial infection; three women whose deaths were reported in the 2006–2008 CMACE report were noted to have either sickle cell disease or sickle trait. An analysis of maternal outcomes in almost 18 000 deliveries by women with sickle cell disease found that there was a significantly higher rate of sepsis in this group (odds ratio 6.8) compared to women without sickle cell disease.[23] This risk may be further compounded by the presence of anaemia.[24] Sickle cell trait has in the past been viewed as a benign carrier state but there is now evidence that it can be viewed as an intermediate disease phenotype.[25] A study

**Table 3 Risk factors for sepsis in obstetrics**

| |
|---|
| ***Obstetric factors*** |
| • Amniocentesis, and other invasive intrauterine procedures |
| • Cervical suture |
| • Prolonged rupture of membranes |
| • Prolonged labour with multiple (>5) vaginal examinations |
| • Vaginal trauma |
| • Caesarean section |
| • Retained products of conception after miscarriage or delivery |
| ***Patient factors*** |
| • Obesity |
| • Impaired glucose tolerance/diabetes |
| • Impaired immunity |
| • Anaemia |
| • Vaginal discharge |
| • History of pelvic infection |
| • History of Group B streptococcal infection |

of maternal outcomes amongst haemoglobinopathy carriers found an increased risk of bacteriuria in women with sickle sell trait.[26]

The causes of sepsis in obstetrics may be divided into obstetric and other causes (Table 4). In early pregnancy the commonest causes of sepsis are septic abortion or termination of pregnancy. Caesarean section endometritis used to be a major cause of postpartum infection with the incidence of sepsis following operative delivery once being as high as 36%.[27] Women undergoing caesarean section still have a five- to 20-fold greater risk for infection and infectious morbidity compared with a vaginal birth.[28] A cohort study from Denmark of over 32 000 women compared the risk of postpartum infections within 30 days of delivery, following vaginal delivery, or emergency or elective caesarean section. The risk of postpartum infection for all women delivered by caesarean section was 7.6%, versus 1.6% for women who had a vaginal delivery (adjusted odds ratio 4.71).[29] Routine antibiotic prophylaxis at caesarean section was in place during the study period and therefore even with this precaution, infection was five times more likely in women who delivered by caesarean section rather than vaginal delivery. The authors also found a nearly 50% higher risk of postpartum wound infection after emergency caesarean section compared to elective caesarean section (odds ratio 1.49).

Smaill and Gyte[28] reviewed 86 studies involving over 13 000 women. They found prophylactic antibiotics in women undergoing caesarean section substantially reduced the incidence of febrile morbidity, wound infection, endometritis and serious maternal infectious complications. The mandatory use of prophylactic antibiotics at caesarean section has been a recommendation for some time. However, the timing of prophylactic antibiotics has recently been the subject of some discussion.[30] Largely because of concerns about neonatal infection, the prevailing UK practice has been to use narrow-range antibiotics after cord clamping, compared to the practice of broad-spectrum pre-incision antibiotics which is standard in non-obstetric surgery. A recent meta-analysis suggests the latter approach may be more effective in reducing infections after caesarean section, without any detrimental effect on the neonate.[31] The American College of Obstetricians and Gynecologists recommends this strategy[32] and in the UK the recently published National Institute for Clinical Excellence Caesarean Section Guideline Update has also made similar recommendations.[33] The appropriate and optimal antibiotic for prophylaxis also remains unclear.[34] A Cochrane review found there was no conclusive evidence of any outcome difference between cephalosporins and penicillins in regard to maternal sepsis, endometritis, fever, wound infection, urinary tract infection and adverse effects.[35]

It has been estimated that after vaginal delivery mastitis and urinary tract infections are the commonest causes of infection.[36] Mastitis affects up to 20% of postpartum women but is comparatively rare as a cause of postpartum sepsis.[37] As a result of the physiological and anatomical changes of pregnancy within the urinary tract there is increased susceptibility to urinary tract infection and urosepsis. There is renal pelvic and ureteric dilatation secondary to mechanical obstruction by the gravid uterus. Progesterone-induced smooth muscle relaxation leads to decreased peristalsis of the ureters, increased bladder capacity and urinary stasis. Asymptomatic bacteriuria has an incidence in pregnancy of between 4–6% but it has been estimated that if left untreated as many as 20–40% will go on to develop pyelonephritis.[38,39] After delivery the prevalence of urinary tract infections remains significant at around 2–4%. The presence of a urinary catheter in association with caesarean delivery and/or neuraxial analgesia increases the risk.[40]

**Table 4 Causes of sepsis in obstetrics**

| |
|---|
| ***Obstetric causes*** |
| Genital tract causes |
| • Chorioamnionitis |
| • Endometritis |
| • Septic abortion |
| • Wound infection following caesarean section/episiotomy/ vaginal tear |
| **Non-genital tract causes** |
| • Lower urinary tract infection |
| • Pyelonephritis |
| • Breast infection – abscess/mastitis |
| • Septic pelvic thrombophlebitis |
| ***Non-obstetric causes*** |
| • Human immunodeficiency virus |
| • Pneumonia |
| • Tuberculosis |
| • Malaria |

## Microbiology

The genitourinary tract is colonised with a wide variety of organisms; however, not all of these cause infection and sepsis. Pregnant women who develop sepsis are very likely to be infected with more than one organism. Analysis of the microbiological causes of deaths from sepsis (direct and indirect) over the last 20 years of the UK Confidential Enquiry is shown in Table 5.

Historically, although they were not characterised serologically by Rebecca Lancefield until 1933, it seems likely that Group A streptococcus was the predominant cause of obstetric sepsis in the first-half of the 20th century.[6,9] Outbreaks were frequently described, particularly when scarlet fever was also prevalent. In the latter part of the 20th century factors such as improved

**Table 5 Microbiological causes of maternal death identified in UK Confidential Enquiries 1991–1993 to 2006–2008**

| | 1991–1993 | 1994–1996 | 1997–1999 | 2000–2002 | 2003–2005 | 2006–2008 | Total |
|---|---|---|---|---|---|---|---|
| β haemolytic streptococcus Lancefield group A | 1 | 7 | 3 | 3 | 8 | 13 | 35 |
| Escherichia coli | 2 | 3 | 6 | 2 | 7 | 5 | 25 |
| Streptococcus pneumoniae | | 3 | 4 | 2 | 5 | 3 | 17 |
| Human immunodeficiency virus | | | 1 | 4 | 5 | 2 | 12 |
| Staphylococcus aureus | | | 1 | 3 | 2 | 4 | 10 |
| Streptococcus unspecified | 5 | 3 | | | | | 8 |
| Clostridium species | 1 | 1 | 1 | 1 | | 1 | 5 |
| β haemolytic streptococcus Lancefield group B | | 2 | | 2 | 1 | | 5 |
| Tuberculosis | | | | | 4 | 2 | 6 |
| Pseudomonas | 1 | | | | 3 | | 4 |
| Proteus species | 2 | | | | 2 | | 4 |
| Meningococcus | | 1 | 1 | 1 | | | 3 |
| Toxoplasmosis | | 2 | 1 | | | | 3 |
| Enterococcus faecalis | | | 1 | | | 1 | 2 |
| Varicella | | 1 | 1 | | | | 2 |
| β haemolytic streptococcus Lancefield group C | | | 1 | | | | 1 |
| β haemolytic streptococcus Lancefield group D | | | | 1 | | | 1 |
| Morganella | | | | | | 1 | 1 |
| Actinobacter | | | | | 1 | | 1 |
| Listeria | | | | | 1 | | 1 |
| Citrobacter kosseri | | | | | 1 | | 1 |
| Fusobacterium necrophorum | | | | 1 | | | 1 |
| Bacteroides melaminogenicus | 1 | | | | | | 1 |

Data from direct and indirect causes combined for each triennium. Number of deaths may not equal actual number of deaths from reports as full microbiological data not always available.

antiseptic techniques, the use of antibiotics and an increase in natural immunity lead to a decline in the virulence of this organism. Gram-negative organisms such as Escherichia coli then became more common sources of infection. However, over the past 20 years gram-positive organisms, and in particular group A streptococcal infections, have again become predominant. This is consistent with the pattern of group A streptococcal infections in the general population of the developed world, where there has been a dramatic rise in the number of such infections.[41,42] In the most recent UK CMACE Report, group A streptococcal infections accounted for 13 of the 29 deaths. In this report the majority of the deaths were noted to occur between December and April, and in many of those who died there was a history of a recent upper respiratory tract infection and/or of contact with young children. Group A streptococcal upper respiratory tract infections are most common during winter and early spring. In contrast group A streptococcus as a cause of skin infections is seen more frequently during the summer, when the skin is exposed and abrasions and insect bites are more likely to occur.

In the developing world there are more limited data on the specific microbiological causes of obstetric sepsis. Available evidence suggests a similar pattern of bacterial causes to that in the developed world.[43] However, in recent times the HIV/AIDS pandemic has undoubtedly been the most important factor with regard to sepsis-related maternal morbidity and mortality in the developing world. A major WHO analysis assessing progress towards the Millennium Development Goal of reducing maternal mortality, found that in 2008 there were an estimated 342 900 maternal deaths worldwide from all causes, a 34% decline from 1980.[44] It is estimated that HIV accounted for 61 400 of these deaths. The impact of this disease was greatest in sub-Saharan Africa, where WHO estimates for 2008 suggest that without HIV/AIDS related deaths, the maternal mortality ratio for sub-Saharan Africa would have been 580 maternal deaths per 100 000 live births instead of the actual figure of 640.[45]

Pregnant women with HIV/AIDS are more susceptible to sepsis and post-surgical complications. Many opportunistic infections associated with HIV/AIDS may complicate pregnancy and cause maternal mortality.[46] Pneumocystis jirovecii (previously carinii) pneumonia has a more aggressive course during pregnancy, with an increase in both morbidity and mortality.[47] The South African Confidential Enquiry into Maternal Deaths, Saving Mothers, found that bacterial pneumo-

nias, bacterial sepsis, atypical pneumonia, cryptococcal meningitis, and tuberculosis (TB) are common co-morbid conditions associated with HIV/AIDS, and may be the primary causes of maternal death in that country.[48] Worldwide the most significant infection contributing to maternal mortality in HIV-infected women is TB. It accounts for about 700 000 deaths annually in women of reproductive age,[49] and is by far the most common opportunistic infection associated with HIV in the developing world. A five-year review of maternal mortality at a tertiary referral centre in Johannesburg found that mortality in HIV-infected women was 6.2 times greater than in HIV-negative women and that 31% of HIV-related deaths were due to TB.[50]

Postnatal care is often poor in African countries, and puerperal sepsis is a major cause of maternal mortality.[51] It has been suggested that the impact of puerperal sepsis could be significantly reduced if, following delivery, women were to remain in hospital for at least 24 h, and/or improved arrangements were put in place for postnatal follow-up. Clinical experience suggests that HIV-infected women may be clinically well at the time of early discharge, only to be re-admitted with florid sepsis 7–10 days after delivery.[48]

## Clinical presentation and diagnosis

Sepsis is a clinical diagnosis and microbiological investigations may be negative. The onset of sepsis may be insidious and non-specific, particularly given the physiological changes of pregnancy, labour and the puerperium. Diagnosis can therefore be difficult, especially in the early stages. Conversely the disease process can be fulminant, overwhelming and rapidly fatal.[52–54] The clinician must often rely on a high index of clinical suspicion rather than objective criteria. Women at risk of infection, such as those colonised with Group B streptococcus, should be identified early in pregnancy.

Initially infection may present with localised symptoms and signs; the presenting features vary depending on the source of infection (Table 6) and a careful clinical history may help clarify the source. Maternal infection can rapidly affect the fetus; the uteroplacental circulation does not exhibit autoregulation, so that fetal perfusion and oxygenation is dependent on maternal oxygenation and cardiovascular stability. Thus the septic woman may present with an abnormal fetal heart rate pattern or intrauterine fetal death.

Women will invariably experience some degree of pain following caesarean section or significant vaginal tears. However, the presence of constant, severe abdominal or perineal pain, poorly responsive to analgesics and disproportionate to that which would be anticipated, is a cause for concern, particularly when it is associated with diarrhoea, and sepsis must then always be considered in the differential diagnosis.[1] When mastitis that does not respond to conservative management within 24 h, and the woman is becoming systemically unwell, then the breasts must be considered as a possible source of sepsis.

The onset of sepsis is characterised by a hyperdynamic circulation, reduced systemic vascular resistance secondary to arterial vasodilatation, and increased respiratory rate in association with the development of anaerobic metabolism and lactic acidosis. Therefore when sepsis develops not only can diagnosis be made more difficult because of the physiological changes of pregnancy, but in addition the combined effect of pathological processes superimposed on a state of increased physiological demand may result in a particularly severe disease burden.

**Table 6 Symptoms and signs of sepsis**

***Symptoms***

General
- Fever
- Influenza-like symptoms
- Sore throat
- Diarrhoea
- Vomiting
- Shortness of breath
- Wound infection

Specific
- Premature contractions
- Abdominal pain
- Sickle cell crisis
- Atonic uterus precipitating postpartum haemorrhage
- Mastitis
- Vaginal discharge – profuse and/or malodorous

***Signs***
- Pyrexia or hypotheremia, <36°C
- Early pregnancy loss/abnormal fetal heart rate/death in utero
- Tachycardia >100 beats/min
- Tachypnoea >20 breaths/min
- Elevated white cell count and neutrophilia or low white cell count/neutropenia
- Rising C-reactive protein (CRP)
- Lactic acidosis
- Signs of organ decompensation: hypoxaemia; hypotension; cool extremities; reduced capillary refill; oliguria

Pyrexia is common in sepsis but normothermia may also be present. Hypothermia is a particularly significant finding. Swinging pyrexia suggests a persistent source of infection or inadequate treatment.[1] Although an elevated white cell count is commonly associated with sepsis, pregnancy also leads to an increase in white cell count, particularly during labour. After delivery the white cell count usually decreases to pre-pregnancy levels within a week; a white cell count that fails to decrease to normal levels or conversely decreases rapidly or becomes $<4 \times 10^9$/L may indicate severe infection. One of the most sensitive and earliest clinical signs of sepsis is tachypnoea which arises as a result of pyrexia, lactic acidosis or cytokine-mediated effects on the respiratory centre. The overlapping physiological changes of pregnancy and clinical features of sepsis will often pose diagnostic difficulty and the existence of a suitable biomarker in this context would be particularly useful. In the intensive care community there has been significant interest in the use of biomarkers to help establish a diagnosis of sepsis. Much of this discussion has focused on procalcitonin, a peptide precursor of the hormone calcitonin and is produced by the parafollicular cells of the thyroid and the neuroendocrine cells of the lung and the intestine. Procalcitonin levels rise specifically in the presence of bacterial but not viral or fungal sepsis.[55] Therefore laboratory measurement of procalcitonin levels can potentially assist with diagnosis. However, meta-analyses have produced conflicting results on whether procalcitonin is an effective and useful sepsis biomarker.[56,57] A recent comprehensive review states that clinical judgement should remain the cornerstone of clinical decision-making. A more encouraging role for procalcitonin is its measurement to guide duration of antibiotic therapy.[58]

## Management and the Surviving Sepsis Campaign

Management of the septic pregnant patient follows the same principles as that of any septic patient: resuscitation, identification and treatment of the source of sepsis, management of complications such as hypotension and tissue hypoxia, and the application of organ protection strategies. The management of sepsis arising in the antenatal period is complicated by the presence of the fetus; in this situation maternal resuscitation is key to ensuring fetal well-being,[59] and attempting early delivery in women with cardiovascular compromise due to sepsis may increase maternal and fetal mortality.[60] The only exception is when intrauterine infection is suspected as the source of sepsis.[61]

Early recognition of the obstetric patient with sepsis is key to ensuring optimal outcome. As noted previously, the physiological changes of pregnancy can make early detection difficult and at the same time exacerbate the course of sepsis in an obstetric patient. The use of early warning scores was a recommendation in the 2003–2005 UK Confidential Enquiries into Maternal Deaths.[22] Clear evidence of outcome benefit is, however, lacking, with one major study on the use of early warning scores and medical response teams in the non-obstetric hospital population failing to demonstrate a reduction in mortality, though this has been attributed to a possible lack of sensitivity in the criteria used for triggering clinical calls.[62] The importance of developing maternity early warning scores with appropriately sensitive parameters for use in obstetric patients has been emphasised by a recent retrospective review.[63]

Recommendations from the Royal College of Obstetricians and Gynaecologists (RCOG) are that sepsis should be managed in accordance with the Surviving Sepsis Campaign guidelines.[64] This campaign, a collaboration between the European Society of Intensive Care Medicine, the Society of Critical Care Medicine and the International Sepsis Forum, was launched as a major international health initiative in 2002.[65] It aimed to improve outcome in sepsis and advocated a standardised bundle-based approach for management of the (non-pregnant) critically-ill septic patient. A clinical-care bundle is a set of interventions, usually no more than five, that when grouped and implemented together lead to better outcomes with a greater impact than if performed individually. The elements in a bundle are ideally based on high quality or level-one evidence such as systematic reviews of multiple well-designed randomized controlled trials. In clinical practice, the application of these elements may not always be done consistently, leading to variations in patient care, so a bundle aims to tie the care elements together into a cohesive unit that must be strictly adhered to for every patient, every time. Lastly all the components of a clinical-care bundle must be completed in a specified time period and place ('the golden hour.') Compliance is measured in an 'all or none' approach.[66]

The Surviving Sepsis Campaign guidelines described two clinical-care bundles - the resuscitation bundle (to be accomplished as soon as possible) and the management bundle. The RCOG advocates the use of these in obstetrics.[64]

The following care bundle should be applied immediately where possible or within six hours and has been shown to significantly improve survival rates[67]

1. Measure serum lactate.
2. Obtain blood cultures/swab culture before antibiotic administration.
3. Administer broad-spectrum antibiotic(s) within the first hour of recognition of severe sepsis and septic shock according to local protocol

4. In the event of hypotension and/or lactate >4 mmol/L:
   (a) deliver an initial minimum of 20 mL/kg of crystalloid or colloid
   (b) once adequate volume replacement has been achieved, a vasopressor (e.g. norepinephrine, epinephrine) and/or an inotrope (e.g. dobutamine) may be used to maintain mean arterial pressure over 65 mmHg.

5. Further management consists of:
   (a) In the event of ongoing hypotension despite fluid resuscitation (septic shock) and/or lactate >4 mmol/L:
      (i) achieve a central venous pressure of at least 8 mmHg (or over 12 mmHg if the woman is mechanically ventilated) with further fluid replacement
      (ii) consider steroids.

   (b) Maintain oxygen saturation with facial oxygen. Consider transfusion if haemoglobin is <7 g/dL.

Antibiotic therapy via the intravenous route and in high therapeutic doses should be started as early as possible, and preferably within one hour. There is overwhelming evidence that delay in starting antibiotics is associated with increased mortality,[68] and this has consistently been cited as an area of substandard care in successive UK confidential enquiries. Causes of delay include errors in administration, prescription errors, patients awaiting senior review and patients being transferred between departments; strenuous efforts must be made to avoid such delays.[69] Relevant swabs and cultures should be taken before antibiotic therapy is started but should not delay treatment. Where applicable these should include placental and neonatal swabs, as well as breast milk culture in the presence of mastitis. Broad-spectrum antibiotics should be used initially and two or more agents are likely to be needed.[70,71] Urgent microbiological advice should be sought as soon as possible but should not delay starting antibiotics. The physiological changes of pregnancy, including the increased volume of distribution, which can also be increased in sepsis, can have an effect on the pharmacodynamic and pharmacokinetic profile of the drug. Some women may have impaired renal or hepatic function and serum drug levels may need to be monitored to ensure correct dosage. However the appropriate loading dose when starting antibiotic therapy is independent of the patient's renal function and the initial loading dose is particularly important to ensure appropriate serum concentrations of drugs.[72]

Regular reassessment of antibiotic therapy should occur in relation to the patient's clinical condition. Treatment should be for a minimum of 7–10 days and it is essential that treatment is not discontinued too soon.[1,22] The most recent UK CMACE report suggested a stratified approach to antibiotics in sepsis (Table 7);[1] antibiotic regimens should be altered to adapt to the requirements of the local population and the particular clinical situation of the patient.

In addition to starting antibiotic therapy it is essential that any septic focus is identified and removed wherever feasible. This may require urgent surgery and appropriate imaging and surgical opinion should be undertaken as soon as possible.

Early haemodynamic resuscitation is a key goal of therapy.[74,75] The objective is to restore adequate oxygen delivery to peripheral tissues. It is well recorded that in high-risk surgical patients with sepsis, early haemodynamic optimisation before, as opposed to after, the development of organ failure reduces mortality by 23%.[76,77] In hypotensive septic patients with a serum lactate >4 mmol/L volume resuscitation should be used ini-

**Table 7 Suggested intravenous antibiotic therapy in obstetric sepsis**

Where the organism is unknown and the woman is not critically ill:
- Co-amoxiclav 1.2 g 8-hourly or cefuroxime 1.5 g 8-hourly or cefotaxime 1–2 g 8-hourly or 6-hourly plus metronidazole 500 mg 8-hourly
- In cases of allergy to penicillin and cephalosporins, use clarithromycin 500 mg 12-hourly or clindamycin 600 mg to 1.2 g 8-hourly or 6-hourly plus gentamicin to give Gram-negative cover, while waiting for microbiological advice

In severe sepsis or septic shock:
- Piperacillin–tazobactam 4.5 g 8-hourly or ciprofloxacin 600 mg 12-hourly plus gentamicin 3–5 mg/kg daily in divided doses every 8 hours[a]
- A carbapenem such as meropenem 500 mg to 1 g 8-hourly +/− gentamicin
- Metronidazole 500 mg 8-hourly may be considered to provide anaerobic cover
- If Group A streptococcal infection is suspected, clindamycin 600 mg to 1.2 g three or four times daily, 8-hourly is more effective than penicillins

If there are risk factors for MRSA septicaemia, add teicoplanin 10 mg/kg 12-hourly for three doses, then 10 mg/kg 24-hourly or linezolid 600 mg 12-hourly

MRSA, methicillin-resistant staphylococcus aureus.
[a] Gentamicin is more commonly given as a once daily dose because of increased efficacy and reduced nephrotoxicity.[73]

tially, aiming to reach the following clinical endpoints: central venous pressure 8–12 mmHg, mean arterial pressure 65 mmHg, and a urine output of 0.5 mL/kg/h. If measurable, a central venous oxygen saturation of >70% should be aimed for. There is no evidence to support one type of intravenous fluid over another.[78] Vasopressor support may be considered even before optimal intravenous loading has been achieved.[79] Transfusion of red blood cells may be necessary if tissue oxygen delivery still remains inadequate.[80]

Fluid management is difficult in sepsis and may be particularly so in the severely ill obstetric patient: fluid overload leading to pulmonary oedema has contributed to the deaths of some women in UK Confidential Enquiries Reports.[1] There are various reasons why the obstetric patient may be vulnerable to fluid overload: the physiological changes of pregnancy are such that at term the parturient is already in a relatively volume overloaded state; co-morbidity such as preeclampsia may be present and uterotonic drugs that are known to predispose to fluid retention (e.g. oxytocin) or pulmonary oedema (e.g. carboprost) may have. Oesophageal Doppler monitoring to guide intravenous fluid therapy has recently been endorsed by the National Institute for Clinical Health and Excellence.[81] Although this report did not assess its use in obstetric patients, the oesophageal Doppler has been used successfully in the obstetric emergency situation,[82] and it would seem likely and appropriate that this minimally invasive technique should become increasingly used in obstetric practice.

Supplemental oxygen therapy is recommended even if there is no respiratory distress. Tracheal intubation and ventilation should be considered if the level of consciousness is low or if there is hypoxia or progressive respiratory distress.[83]

Necrotising fasciitis is a surgical emergency. It has been described in association with caesarean section,[84] and can present as a perineal infection after vaginal delivery.[85] It is characterized by widespread necrosis of subcutaneous tissue and fascia and is most commonly associated with group A streptococcal infection, although a mixed bacterial flora including anaerobes is often present. In the early stages it may be difficult to distinguish between cellulitis and necrotising fasciitis. Distinguishing features include the presence of copious and malodorous discharge, dusky skin discolouration, markedly severe pain and radiological or clinical evidence of gas in the soft tissues.[86]

## Role of the anaesthetist

The anaesthetist may have a pivotal role in the management of the severely septic parturient.[87] In UK practice acute management and stabilisation of the septic obstetric patient in the maternity unit, is most often conducted by the obstetric anaesthetic team. The initial multidisciplinary 'golden hour' of immediate treatment needs to be guided by using a specially adapted sepsis bundle written for the parturient.[64] If the patient does not respond rapidly and the decision is made to escalate to level-3 critical care, this transfer should be carried out by an appropriately skilled doctor. Transfer of the critically septic patient requires satisfactory stabilisation, rigorous en-route monitoring and close communication with the receiving unit. Lack of early and precise communication between specialties is an ongoing problem with clinicians involved with obstetric emergencies, and the anaesthetist is often best placed to communicate between the various teams involved.[1,22]

Decisions relating to the delivery of the baby are ultimately the responsibility of the obstetrician, although the obstetric anaesthetist may be able to advise on the timing in relation to maternal resuscitation. The anaesthetist then has to make a decision about whether to perform surgery using neuraxial or general anaesthesia. It is generally agreed that neuraxial anaesthesia is relatively contraindicated in patients with severe sepsis. The biggest concerns are the supposed increased risk of epidural abscess or meningitis. Quantifying these risks is difficult - the white cell count increases in pregnancy and particularly during labour,[88] and there is little correlation between white cell count and the presence of bacteraemia in pregnancy.[89]

Epidural abscess in association with neuraxial blockade can occur as a result of direct introduction of microorganisms on the needle, via local infection at the puncture site, contaminated fluids or the epidural catheter acting as a foreign body and a nidus for infection in the presence of bacteraemia. Spontaneous cases unrelated to neuraxial anaesthesia are also described and while underlying medical conditions such as diabetes can increase risk, epidural abscesses have also occurred in postpartum women without risk factors and who did not receive neuraxial block.[90] The incidence in all patients admitted to hospital has been estimated at 0.2–1.2/10 000.[91] The Third National Audit Project of the Royal College of Anaesthetists found an incidence of 1 in 47 000 cases although the majority of reports occurred in perioperative patients:[92] there was only one report in an obstetric patient. Scott and Hibbard in a retrospective review found only one case in 505 000 women who received epidural anaesthesia for vaginal delivery or caesarean section.[93] An incidence of 3% has been quoted in patients who had epidural catheters inserted for chronic pain procedures.[94] Similarly there are several case reports in the literature of meningitis following spinal and epidural anaesthesia and also epidural blood patches,[95–97] but it is difficult to draw firm conclusions from isolated reports. Common features to these reports include difficult procedures, multiple attempts and epidural catheters remaining in situ for extended periods.

In 2004 the American Society of Regional Anesthesia and Pain Medicine convened a Practice Advisory Panel on the Infectious Complications Associated with Regional Anesthesia and Pain Medicine who produced a series of practice guidelines.[98,99] All patients with local or systemic infection who require neuraxial anaesthesia should be considered at risk of central nervous system infection. The current evidence suggests that patients with evidence of systemic infection may safely receive spinal anaesthesia provided the patient has been commenced on antibiotics and shows a response to treatment. Regarding epidural insertion, evidence is limited to very small studies in women with chorioamnionitis which suggests that it may be safe in similar circumstances. Only in the most unusual circumstances should central neural blockade be performed in patients with untreated systemic infection.

Two final points to consider in relation to neuraxial anaesthesia and sepsis are that a septic hypotensive patient may not tolerate the sympathetic blockade and that coagulopathy may have developed. Ultimately the decision to perform an epidural or spinal in these circumstances must be considered on a case-by-case basis, assessing the risk-benefit ratio for that individual.

General anaesthesia may often be indicated and once achieved this can facilitate initiating invasive vascular monitoring and inotropic support, if indicated. Decisions as to the reversal of general anaesthesia will depend on the stability of the patient. It may be safer to first transfer the intubated, ventilated patient under ongoing sedation to a more appropriate environment.

Not uncommonly radiological imaging will need to be undertaken to help identify the source of sepsis and this should only occur in the stabilised patient. Early removal of the source of sepsis is recommended whenever possible and suitably cross-matched blood and blood products may be required before and during surgery.

## The future

Sepsis is a major cause of morbidity and mortality worldwide and a huge amount of work has been directed at improving the outcome of this condition. The management of sepsis in obstetric practice is likely to benefit from this work. The UK Obstetric Surveillance System is running a two year population-based case-control study to investigate the incidence, associated risk factors and management and outcomes of severe maternal sepsis which will provide valuable information.[100] The RCOG are due to publish their own guidelines soon. Recommendations from the most recent UK CMACE report emphasize the importance of early recognition of and response to the septic obstetric patient in a 'back-to-basics' manner.

## References


1. Centre for Maternal and Child Enquiries (CMACE). Saving Mothers' Lives: Reviewing maternal deaths to make motherhood Safer: 2006–2008. The Eighth Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG* 2011;**118**(Suppl. 1):1–203.
2. Dolea C, Stein C. Global Burden of disease 2000. http://www.who.int/healthinfo/statistics/bod_maternalsepsis.pdf accessed June 2011.
3. Scottish NHS Quality Improvement Scotland. Scottish Confidential Audit of Severe Maternal Morbidity. 6th Annual Report. Edinburgh. NHS QIS; 2010.
4. Baskett TF, Sternadel J. Maternal intensive care and near-miss mortality in obstetrics. *BJOG* 1998;**105**:981–4.
5. Loudon I. *Death in Childbirth: an International Study of Maternal Care and Maternal Mortality 1800–1950*. Oxford: Clarendon Press; 1992.. p. 258–261.
6. Drife J. Infection and maternal mortality. In: Maclean AB, Regan L, Carrington D, editors. *Infection and pregnancy*. London: RCOG Press; 2001. p. 355–64.
7. Gordon A. *A treatise on the epidemic puerperal fever of Aberdeen*. London: GG and J Robinson; 1795.
8. Holmes OW. The contagiousness of puerperal fever. *N Engl J Med* 1843;**1**:503.
9. Steer P. Puerperal sepsis. In: Chamberlain G, Steer P, editors. *Turnbull's obstetrics*. 3rd ed. Edinburgh: Churchill Livingstone; 2001. p. 663–70.
10. Gould I. Alexander Gordon, puerperal sepsis, and modern theories of infection control—Semmelweis in perspective. *Lancet Infect Dis* 2010;**10**:275–8.
11. Ministry of Health. Report on an Investigation into maternal mortality. London: HMSO; 1937.
12. Ministry of Health. Report on Confidential Enquiries into Maternal Deaths in England and Wales, 1952–4. London: HMSO, 1957. Ministry of Health Reports on Public Health and Medical Subjects No 97.
13. Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look P. WHO systematic review of causes of maternal deaths. *Lancet* 2006;**367**:1066–710.
14. World Health Organisation. The prevention and management of puerperal infections. Report of a technical working group. Division of Family Health, Maternal Health and Safe Motherhood Programme Geneva 1992. http://www.whqlibdoc.who.int/hq/1995/WHO_FHE_MSM_95.4.pdf accessed June 2011.
15. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992;**101**:1644–55.
16. Mor G, Cardenas I. The immune system in pregnancy: a unique complexity. *Am J Reprod Immunol* 2010;**63**:425–33.
17. Mor G, Cardenas I, Abrahams V, Guller S. Inflammation and pregnancy: the role of the immune system at the implantation site. *Ann N Y Acad Sci* 2011;**1221**:80–7.
18. Wilson RC. Immune problems in pregnancy. In: Russell IF, Lyons G, editors. *Clinical problems in obstetric anaesthesia*. London: Chapman and Hall Medical; 1997. p. 103–22.
19. Szekeres-Bartho J. Immunological relationship between the mother and the fetus. *Int Rev Immunol* 2002;**21**:471–95.
20. Okoko BJ, Enwere G, Ota MO. The epidemiology and consequences of maternal malaria: a review of immunological basis. *Acta Trop* 2003;**87**:193–205.
21. Maharaj D. Puerperal pyrexia: a review. Part I. *Obstet Gynecol Surv* 2007;**62**:393–9.
22. Lewis G, editor. *The Confidential Enquiry into Maternal and Child Health (CEMACH). Saving Mothers Lives: Reviewing maternal*

*deaths to make motherhood safer 2003–2005. The Seventh Report on Confidential Enquiries into Maternal Deaths in the United Kingdom*. London: CEMACH; 2007.
23. Villers MS, Jamison MG, De Castro LM, James AH. Morbidity associated with sickle cell disease in pregnancy. *Am J Obstet Gynecol* 2008;**199**:125.e1–5.
24. Dare FO, Bako AU, Ezechi OC. Puerperal sepsis: a preventable post-partum complication. *Trop Doct* 1998;**28**:92–5.
25. Key NS, Derebail VK. Sickle-cell trait: novel clinical significance Hematology. *Am Soc Hematol Educ Program* 2010;**2010**:418–22.
26. Tsaras G, Owusu-Ansah A, Boateng FO, Amoateng-Adjepong Y. Complications associated with sickle cell trait: a brief narrative review. *Am J Med* 2009;**122**:507–12.
27. Sweet RL, Ledger WJ. Puerperal infectious morbidity: a two-year review. *Am J Obstet Gynecol* 1973;**117**:1093–100.
28. Smaill FM, Gyte GML. Antibiotic prophylaxis versus no prophylaxis for preventing infection after cesarean section. *Cochrane Database Syst Rev*(1):CD007452.
29. Leth RA, Moller JK, Thomsen RW, Uldbjerg N, Norgaard M. Risk of selected postpartum infections after cesarean section compared with vaginal birth: A five-year cohort study of 32,468 women. *Acta Obstet Gynecol Scand* 2009;**88**:976–83.
30. Camann W, Tuomala R. Antibiotic prophylaxis for cesarean delivery: always before skin incision! *Int J Obstet Anesth* 2011;**20**:1–2.
31. Costantine MM, Rahman M, Ghulmiyah L, et al. Timing of perioperative antibiotics for caesarean delivery: a metaanalysis. *Am J Obstet Gynecol* 2008;**199**:301.e1–6.
32. American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 465: Antimicrobial prophylaxis for caesarean delivery: timing of administration. *Obstet Gynecol* 2010;**116**:791–2.
33. National Institute for Clinical Health and Exellence. Caesarean Section Guideline update http://www.nice.org.uk/nicemedia/live/13620/57162/57162.pdfaccessed November 2011.
34. Lamont R, Sobel J, Kusanovic J, et al. Current debate on the use of antibiotic prophylaxis for caesarean section. *BJOG* 2011;**118**:193–201.
35. Alfirevic Z, Gyte GML, Dou L. Different classes of antibiotics given to women routinely for preventing infection at caesarean section. Cochrane Database Syst Rev 2010;(10):Cd008726.
36. Yokoe DS, Christiansen CL, Johnson R, et al. Epidemiology of and surveillance for postpartum infectious. *Emerg Infect Dis* 2001;**7**:837–41.
37. Kinlay J, O'Connell D, Kinlay S. Incidence of mastitis in breastfeeding women six months after delivery: a prospective cohort study. *Med J Aust* 1998;**169**:310–2.
38. Macejko AM, Schaeffer AJ. Asymptomatic bacteriuria and symptomatic urinary tract infections during pregnancy. *Urol Clin North Am* 2007;**34**:35–42.
39. Gilstrap LC, Ramin SM. Urinary tract infections during pregnancy. *Obstet Gynecol Clin North Am* 2001;**28**:581–91.
40. Stray-Pdersen B, Blakstad M, Bergan T. Bacteriuria in the puerperium. Risk factors, screening procedures, and treatment programs. *Am J Obstet Gynecol* 1990;**162**:792–7.
41. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal disease. *Lancet Infect Dis* 2005;**5**:685–94.
42. Abouzeid H, Wu P, Mohammed N, Al-Samarrai M. Group A streptococcal puerperal sepsis: the return of a potentially fatal disease. *J Obstet Gynaecol* 2005;**25**:806–8.
43. Akram S, Hossain A, Shamsuzzaman AKM, et al. Aerobic bacterial pattern in puerperal sepsis. *Bangladesh J Med Microbiol* 2008;**2**:22–7.
44. Hogan MC, Foreman KJ, Naghavi M, et al. Maternal mortality for 181 countries, 1980–2008: a systematic analysis of progress towards Millennium Development Goal 5. *Lancet* 2010;**375**:1609–23.
45. World Health Authority. Trends in maternal mortality 1990–2008. http://www.whqlibdoc.who.int/publications/2010/9789241500265_eng.pdf accessed May 2011.
46. McIntyre J. Mothers infected with HIV. *Br Med Bull* 2003;**67**:127–35.
47. Ahmad H, Mehta NJ, Manikal VM, et al. Pneumocystis carinii pneumonia in pregnancy. *Chest* 2001;**120**:666–71.
48. National Committee for Confidential Enquiries into Maternal Deaths. Saving Mothers 2005–2007: Fourth Report on Confidential Enquiries into Maternal Deaths in South Africa. Pretoria: National Department of Health, 2009.
49. Mnyani C, McIntyre J. Tuberculosis in pregnancy. *BJOG* 2011;**118**:226–31.
50. Black V, Brooke S, Chersich MF. Effect of human immunodeficiency virus treatment on maternal mortality at a tertiary center in South Africa: a 5-year audit. *Obstet Gynecol* 2009;**114**:292–9.
51. Moodley J, Pattinson R, Baxter C, Sibeko S, Abdool Karim Q. Strengthening HIV services for pregnant women: an opportunity to reduce maternal mortality rates in Southern Africa/sub-Saharan Africa. *BJOG* 2011;**118**:219–25.
52. Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Rapid increase in hospitalisation and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. *Crit Care Med* 2007;**35**:1414–5.
53. Harrison DA, Welch CA, Eddlestone JM. The epidemiology of severe sepsis in England, Wales and Northern Ireland, 1996 to 2004: secondary analysis of a high quality database, the ICNARC Case Mix Programme database. *Crit Care* 2006;**10**:R42.
54. Brun-Buisson C, Doyon F, Carlet J, et al. Incidence, risk factors, and outcome of severe sepsis and septic shock in adults. A multicenter prospective study in intensive care units. French ICU group for Severe Sepsis. *JAMA* 1995;**274**:968–74.
55. Gendrel D, Raymond J, Coste J, et al. Comparison of procalcitonin with C-reactive protein, interleukin 6 and interferon-alpha for differentiation of bacterial vs. viral infections. *Pediatr Infect Dis J* 1999;**18**:875–81.
56. Uzzan B, Cohen R, Nicholas P, Cucherat M, Perret GY. Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: a systematic review and meta-analysis. *Crit Care Med* 2006;**34**:1996–2003.
57. Tang BMP, Eslick GD, Craig JC, McLean AS. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. *Lancet Infect Dis* 2007;**7**:210–7.
58. Kive S, Adams K, Barlow G. Diagnostic and prognostic biomarkers of sepsis in critical care. *J Antimicrob Chemother* 2011;**66**(Suppl. 2):ii33.
59. Paruk F. Infection in obstetric critical care. *Best Pract Res Clin Obstet Gynaecol* 2008;**22**:865–83.
60. Sheffield JS. Sepsis and septic shock in pregnancy. *Crit Care Clin* 2004;**20**:651–60.
61. Casey BM, Cox SM. Chorioamnionitis and endometritis. *Infect Dis Clin North Am* 1997;**11**:203–22.
62. Hillman K, Chen J, Cretikos M, et al. Introduction of the medical emergency team (MET) system: a cluster-randomised controlled trial. *Lancet* 2005;**365**:2091–7.
63. Lappen JR, Keene M, Lore M, Grobman WA, Gossett DR. Existing models fail to predict sepsis in an obstetric population with intrauterine infection. *Am J Obstet Gynecol* 2010;**203**:573.
64. Maternal Collapse in Pregnancy and the Puerperium, Green top guideline No. 56. GTG56.pdf. accessed June 2011.
65. Levy MM, Dellinger RP, Townsend SR, et al. Surviving Sepsis Campaign. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. *Crit Care Med* 2010;**38**:364–74.
66. Peden CJ, Rooney KD. The science of improvement as it relates to quality and safety in the ICU. *J Intens Care Soc* 2009;**10**:260–4.

67. Gao F, Melody T, Daniels R, Giles S, Fox S. The impact of compliance with 6-hour and 24-hour sepsis bundles on hospital mortality in patients with severe sepsis: a prospective observational study. *Crit Care* 2005;**9**:764–70.
68. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006;**34**:1589–96.
69. Appelboam R, Tilley R, Blackburn J. Time to antibiotics in sepsis. *Crit Care* 2010;**14**:50.
70. Handelsman J, Maki DG. Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis. *Lancet Infect Dis* 2004;**4**:519–27.
71. Guinn DA, Abel DE, Tomlinson MW. Early goal directed therapy for sepsis during pregnancy. *Obstet Gynecol Clin North Am* 2007;**34**:459–79.
72. Pea F, Viale P. Bench to bedside review: Appropriate antibiotic therapy in severe sepsis and septic shock – does the dose matter? *Crit Care* 2009;**13**:214.
73. Murry KR, McKinnon PS, Mitrzyk B, Rybak MJ. Pharmacodynamic characterization of nephrotoxicity associated with once-daily aminoglycoside. *Pharmacotherapy* 1999;**19**:1252–60.
74. Gattimoni L, Brazzi L, Pelosi P, et al. A trial of goal directed hemodynamic therapy in critically ill patients. *N Engl J Med* 1995;**333**:1025–32.
75. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy collaborative group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;**345**:1368–77.
76. Kern JW, Shoemaker WC. Meta-analysis of hemodynamic optimization in high-risk patients. *Crit Care Med* 2002;**30**:1686–92.
77. Russell JA, Walley KR, Gordon AC, et al. Interaction of vasopressin infusion, corticosteroid treatment, and mortality of septic shock. *Crit Care Med* 2009;**37**:811–8.
78. Pinfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R. The SAFE study: a comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004;**350**:2247–56.
79. Annane D, Vigno P, Renault A, et al. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomized trial. *Lancet* 2007;**370**:676–84.
80. Fernandes CJ, Akamine N, DeMarco FVC, De Souza JA, Lagudis S, Knobel E. Red blood cell transfusion does not increase oxygen consumption in critically ill septic patients. *Crit Care* 2001;**5**:362–7.
81. National Institute for Health and Clinical Excellence 2011, Cardio Q-ODM Oesophageal Doppler Monitor. *NICE Medical Technologies 3*. London: National Institute for Health and Clinical Excellence; 2011.
82. Chatterjee DJ, Bukunola B, Samuels TL, Induruwage L, Uncles DR. Resuscitation in massive obstetric haemorrhage using an intraosseous needle. *Anaesthesia* 2011;**66**:306–10.
83. Hayes MA, Timmins AC, Yau EHS. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* 1994;**330**:1712–22.
84. Pauzner D, Wolman I, Abramov L, Lidor A, David MP. Post-cesarean-section necrotizing fasciitis: report of a case and review of the literature. *Gynecol Obstet Invest* 1994;**37**:59–62.
85. Ghandi P, Singh S, Farkas A. Group B streptococcal necrotising fasciitis following normal vaginal delivery. *J Obstet Gynaecol* 2009;**29**:554.
86. Gallup DG, Freedman MA, Meguiar RV, Freedman SN, Nolan TE. Necrotizing fasciitis in gynecologic and obstetric patients: a surgical emergency. *Am J Obstet Gynecol* 2002;**187**:305–10.
87. Eissa D, Carton EG, Buggy DJ. Anaesthetic management of patients with severe sepsis. *Br J Anaesth* 2010;**105**:734–43.
88. Broughton-Pipkin F. Maternal physiology in obstetrics. In: Chamberlain G, Steer P, editors. *Turnbull's obstetrics*. 3rd ed. London: Churchill Livingstone; 2001. p. 71–91.
89. Blanco JD, Gibbs RS, Castaneda YS. Bacteremia in obstetrics: clinical course. *Obstet Gynecol* 1981;**58**:621–5.
90. Kitching AJ, Rice ASC. Extradural abscess in the postpartum period. *Br J Anaesth* 1993;**70**:703.
91. Reihsaus E, Waldbaur H, Seeling W. Spinal epidural abscess: a meta-analysis of 915 patients. *Neurosurg Rev* 2000;**23**:175–204.
92. Cook TM, Counsell D, Wildsmith JAW. Major complications of central neuraxial block: report on the Third National Audit of The Royal College of Anaesthetists. *Br J Anaesth* 2009;**102**:179–90.
93. Scott DB, Hibbard BM. Serious non-fatal complications associated with epidural block in obstetric practice. *Br J Anaesth* 1990;**64**:537–41.
94. Strong WE. Epidural abscess associated with epidural catheterisation: A rare event? Report of two cases with markedly delayed presentation. *Anesthesiology* 1991;**74**:943–6.
95. Lee JJ, Parry H. Bacterial meningitis following spinal anaesthesia for Caesarean section. *Br J Anaesth* 1991;**66**:383–6.
96. Ready LB, Heifer D. Bacterial meningitis in parturients after epidural anesthesia. *Anesthesiology* 1989;**71**:988–90.
97. Harding SA, Collis RE, Morgan BM. Meningitis after combined spinal-extradural anaesthesia in obstetrics. *Br J Anaesth* 1994;**73**:545–7.
98. Hebl JR. The importance and implications of aseptic techniques during regional anesthesia. *Reg Anesth Pain Med* 2006;**31**:311–23.
99. Wedel DJ, Horlocker TT. Regional anesthesia in the febrile or infected patient. *Reg Anesth Pain Med* 2006;**31**:324–33.
100. UK Obstetric Surveillance System. Severe maternal sepsis. http://www.nnpeu.ox.ac.uk/ukoss/current-serveillance/ss accessed July 2011.