

Manuscript title: Maternal sepsis update: current management and controversies

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Contribution to authorship

OG conceived, researched and wrote the first draft. NMS researched and made substantial contributions to the content of the article. MRJ reviewed the article with critical revision of intellectual content. All authors edited and approved the final version.

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Key content

- Sepsis is a leading cause of maternal morbidity and mortality, globally and in the UK.
- In pregnancy and the puerperium, women may be more susceptible to rapid deterioration of illness following an infection.
- Sepsis has a complex pathophysiology and the immunological and cardiovascular adaptations of normal pregnancy may have an adverse impact on the maternal response to infection. Furthermore, physiological changes of pregnancy, which mimic those of sepsis, often delay optimal management.
- 'Bedside' identification of pathogens and their antibiotic resistance patterns may help to improve clinical outcomes.
- Recent updates in sepsis management, areas of controversy and the importance of translational research and clinical trials for pregnancy and the puerperium are discussed.

Learning objectives

- To understand the difficulties of diagnosing sepsis in pregnancy.
- To highlight recent updates, new definitions and controversies of current sepsis management.
- To highlight the potential for research to develop novel biomarkers and therapeutic agents specific to the pregnant woman.

Ethical issues

- Sepsis research involving new technologies differentially benefits high-income countries compared with low-/middle-income countries despite the greatest burden of maternal sepsis being in the latter.
- With the current rapid evolution of omic technology platforms, greater affordability will provide greater accessibility.

Keywords: biomarkers / extracorporeal membranous oxygenation / lactate / maternal sepsis / steroids

[Main text]

[Heading 1] Introduction

Sepsis is a leading cause of maternal morbidity and mortality, globally and in the UK. In both low-/middle-income countries (LMICs) and high-income countries (HICs), the incidence is rising. Increased global awareness is required to enable timely diagnosis and optimal management. Management is currently limited, requiring the application of new diagnostic methods while pursuing research in the obstetric population to establish precision medicine.

Maternal sepsis has been thoroughly addressed by the 2012 Royal College of Obstetricians and Gynaecologists (RCOG) Green-top Guidelines on bacterial sepsis in and following pregnancy.^{1,2} In this article, we aim to provide an update on sepsis definitions and management and to consider points of controversy. We will highlight the burden of maternal sepsis globally and describe the unique physiology of pregnancy, which may confuse the clinical presentation and adversely affect the outcome of sepsis. The Review will focus on recent changes in the assessment and management of maternal sepsis in HICs and consider how advances in research technologies can be harnessed to improve diagnostics and therapies.

[Heading 1] A leading cause of maternal morbidity and mortality

The true global burden of maternal sepsis remains to be determined. Accurate case identification has been hindered by shifting definitions and diagnostic failures; even so, the existing statistics are alarming.

Sepsis is one of the most important causes of maternal death in the UK,³ and there is an 8% risk of mortality across HICs.^{4,5} Morbidity, not insignificant in survivors, has an estimated

Accepted Article morbidity/mortality ratio of 50:1.⁶ The World Health Organization (WHO) reports the prevalence of puerperal sepsis alone in live births as 4.4% (equating to 5.7 million cases per year), with a greater burden in LMICs (7%) than in HICs (1–2%).⁷ The contribution of pregnancy-related sepsis (for example, genitourinary tract, surgical site and mastitis) to maternal mortality is around 11%,⁸ but when all infection sites are evaluated, it may be a contributing factor in up to 25–40% of maternal deaths worldwide.⁹ The majority of the available data relate to patients in the puerperium; more studies evaluating the burden of sepsis in antenatal patients are required. In the UK, ‘all-cause sepsis’ ranks as the sixth leading cause of direct and indirect maternal death; genital tract sepsis is the fourth direct cause.¹⁰

In addition to maternal concerns, the fetus is at increased risk of miscarriage, stillbirth and preterm birth. Infection has been associated with 10–25% of cases of stillbirth in HICs and may be as high as 50% in LMICs.¹¹

[Heading 1] Pathophysiology of sepsis

In its most severe form, sepsis is associated with irreversible multiple organ failure and death. The pathogenesis is highly complex and not completely understood (Figures 1 and 2).^{12,13}

In pregnancy and the puerperium, maternal physiological and immunological adaptations – designed to facilitate development of the fetus – may impair maternal capacity to respond to infection. For example, physiological hyperventilation of pregnancy, understood to be secondary to progesterone, creates a respiratory alkalosis that is countered by an increase in renal bicarbonate excretion. Accordingly, pregnant women may be slightly less able to buffer the metabolic acidosis caused by sepsis.^{14,15} Moreover, key physiological changes, which occur to promote the maintenance of a healthy pregnancy, mimic those of early sepsis, making the diagnosis challenging (Figure 3).¹⁶

[Heading 2] Immunology: the obstetric patient

A greater understanding of the complex immunology at play in pregnancy is slowly evolving. The long-held concept proposed by Medawar¹⁷ of an immunologically tolerant maternal environment to allow for fetal growth and development is shifting. Due to considerable research into the immunology of pregnancy in health and pathology (e.g. recurrent miscarriage, preterm birth and pre-eclampsia), the roles of both the innate and adaptive systems are being unravelled. For example, the expansion of ‘immunosuppressive’ regulatory T cells in healthy pregnancy is implicated in

maintaining immune tolerance.^{18–20} Failure of this has been implicated in the aetiology of recurrent miscarriage and preterm labour. Healthy pregnancy has also been associated with an altered innate immune phenotype and gene expression consistent with a relative state of immunosuppression.²¹

[Heading 2] The cardiovascular system: the obstetric patient

Significant morbidity is associated with the cardiovascular changes that occur during septic shock. Endothelium-derived nitric oxide is upregulated in sepsis and plays a critical role in the regulation of smooth muscle relaxation, vascular tone and vasodilatation.²² In pregnancy, prostaglandins and nitric oxide, upregulated by estradiol, are implicated in the physiological adaptations required to support the developing fetus.²³ This may make pregnant women more susceptible to abrupt hypotension in response to infection, causing tissue hypoperfusion and organ dysfunction.

[Heading 1] Sepsis updates

[Heading 2] Definitions

A universal definition of severe infection is required for global uniformity in the clinical diagnosis. This will enable appropriate management and facilitate accurate incidence reporting, which will influence health strategy and research, and prevent heterogeneity in these areas. Therefore, an updated definition of sepsis and septic shock, Sepsis-3, was published in 2016.²⁴ Since publication, the bedside tools, quick sequential (sepsis-related) organ failure assessment (qSOFA) and the sequential organ failure assessment (SOFA) have been used to aid prognosis and diagnosis of sepsis. However, these are unvalidated in pregnant or puerperal women, and direct application is complicated by the physiological differences of healthy pregnancy.²⁵ This was acknowledged by the international medical research community, and WHO undertook a systematic review and expert consultation, developing an obstetric specific consensus definition in 2017, stating that: “Maternal sepsis is a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or postpartum period.”²⁵

Additionally, the Society of Obstetric Medicine of Australia and New Zealand has proposed obstetrically modified SOFA and qSOFA scores (Tables 1 and 2).²⁶

Sepsis-3 defined septic shock as sepsis associated with vasopressor requirements to maintain a mean arterial pressure (MAP) ≥ 65 mmHg in the absence of hypovolaemia and a serum lactate >2 mmol/l.²³ Currently, these parameters are also applied to pregnancy.

Consequent to expert consultation, the Global Maternal Sepsis Study (GLOSS) was set up in 2017 by WHO to establish identification criteria for pregnant women in LMICs and HICs. GLOSS aims to inform epidemiological studies to develop strategies for prevention, early diagnosis and effective management. The study protocol was released in 2018 and publication of the findings is awaited.

[Heading 2] Prevention

Sepsis prevention is the primary objective and currently antenatal screening is offered nationally in the UK for asymptomatic bacteriuria. The increased risk of infection during the peripartum/postpartum periods has been highlighted in a number of studies, with operative deliveries identified as a significant risk factor.^{1,6} A Cochrane systematic review²⁷ demonstrated a reduction in the incidence of febrile morbidity, wound infection, endometritis and other serious infection-related complications with antibiotic prophylaxis use during caesarean section. This has subsequently been recommended by the National Institute for Health and Care Excellence (NICE).²⁸

Observational studies suggest that the incidence of infection may be as high as 16% following operative vaginal delivery compared with 5.5% for an unassisted vaginal birth.²⁹ In 2018, findings from the ANODE study,³⁰ which investigated the effect of prophylactic antibiotics in the prevention of infection following operative vaginal delivery, demonstrated a 56% reduction in confirmed maternal infection when one dose of intravenous antibiotic was administered a median of 3 hours after delivery. It was also associated with a significant reduction in perineal wound infection.³⁰ These findings, demonstrated in a HIC setting, are convincing and suggest a change to current national guidance would be beneficial.

[Heading 2] Diagnosis

[Heading 3] Modifying early warning scores for pregnant women

The modified early warning score (MEWS) observation chart of key physiological characteristics modified for obstetrics (advocated by the Confidential Enquiry into Maternal and Child Health [CEMACH] 2003–2005)³¹ is a helpful tool to identify the ill patient, but is notoriously nonspecific. A validation study published in 2012³² demonstrated an all-cause obstetric morbidity sensitivity of 89% and specificity of 79%. Albright et al.³³ developed a prognostic tool to identify the obstetric patient with sepsis requiring admission to the intensive care unit (ICU). Adapting the traditional early warning score, they incorporated variables obtained from blood tests (Table 3).³³ These variables

were scored according to variance from normal, and a composite score of ≥ 6 would predict ICU admission with increased performance when compared with each individual variable and two other early warning scores used in US emergency departments.³³ Even greater performance can be envisaged using a similar composite assessment, with better performing biomarkers identified in future studies.

[Heading 3] Tools for improved antimicrobial stewardship

Antibiotic resistance is a global concern. In Europe, 25 000 deaths annually have been attributed to five key antibiotic-resistant bacteria, and it is estimated that a failure to address this issue will result in 10 million deaths globally by the year 2050.³⁴

In 2013, the UK Department of Health published a 5-year national strategy to address the impact of antibiotic resistance.³⁵ It highlights that, in addition to antibiotic stewardship, the development of therapeutic adjuncts is key in the fight against sepsis.

In clinical practice, one of the difficulties confirming a systemic microbial infection is the poor specificity and time-consuming nature of traditional culture and sensitivity methods. Despite being the gold standard,³⁶ only 30–40% of blood cultures will be positive in patients with severe sepsis and a minimum of 24 hours is required before the results are available.³⁶

A number of new technologies are being developed with the potential for fast organism identification and antibiotic resistance patterns, ensuring timely and optimised treatment, while reducing the impact on antibiotic selection pressures.

[Heading 3] Polymerase chain reaction and mass spectrometry

Multiplex polymerase chain reaction (PCR) promises to identify multiple pathogen DNA sequences and their resistance genes, from both positive blood cultures and whole blood samples. However, further evaluation of its clinical performance is required before its widespread implementation.³⁷

Similarly, matrix-assisted laser desorption/ionisation (MALDI) using a time-of-flight (TOF) mass spectrometer can identify a wide spectrum of organisms (bacteria and fungi) from clinical isolates of positive cultures. Key advantages of MALDI-TOF and PCR-based methods are accuracy and speed of analysis. However, they are expensive and may identify non-pathogenic organisms. Currently, NICE recommends the use of PCR in childhood meningitis.³⁸

[Heading 2] Biomarkers

[Heading 3] *C-reactive protein and procalcitonin*

Sepsis biomarkers have been the subject of numerous research studies. They have the potential to perform at a variety of levels: identifying patients at the early stages of sepsis, differentiating sepsis from other non-infectious inflammatory pathologies, predicting clinical severity or outcome and guiding escalation/de-escalation of treatment. The biomarkers predominantly in clinical use are derived from blood and include white cell count (WCC), C-reactive protein (CRP), procalcitonin (PCT) and lactate. WCC and CRP are nonspecific for inflammation versus infection, but PCT appears to be more specific for bacterial infection.^{36,39–41}

A number of PCT assays are available, but a meta-analysis conducted by NICE was unable to provide sufficient evidence to recommend routine use to guide acute treatment during suspected bacterial infection.⁴² The updated Surviving Sepsis Campaign (SSC) guidelines admit that there is low quality of evidence to support recommendation for the use of PCT to guide management,⁴⁰ and caution should be exercised in the extrapolation of this to the pregnant population, particularly in the absence of a normal range.⁴¹

[Heading 3] *Lactate*

Padilla et al¹⁵ recommend using the Sepsis-3 to guide management of patients with sepsis. A venous lactate of >2 mmol/L should prompt critical care input and a level of >4 mmol/L, despite intravenous fluid resuscitation and requiring the use of vasopressors, should lead to the initiation of central venous pressure (CVP) and oxygen saturation monitoring (aiming for a CVP ≥ 8 mmHg and central venous oxygen saturation [ScvO₂] $\geq 70\%$).¹⁵

Lactate levels in normal pregnancy have been assumed to be consistent with those of the general population. However, lactate levels may be elevated as a result of the increased metabolic load of pregnancy; if this is compounded by haemorrhage or sepsis, a pregnant woman's ability to compensate may be compromised.

An elevated serum lactate is associated with a poor outcome in maternal sepsis. In the non-pregnant woman, serum levels of >4 mmol/L alongside clinical evidence of septic shock are associated with mortality rates approaching 46%.^{14,43} Although serum lactate is a good indicator of tissue hypoperfusion and hypoxia, direct measurement of metabolic acidosis should also be considered.²⁶

[Heading 2] Bundles of care

In 2001, a study comparing a protocolised care bundle for sepsis with standard care demonstrated an improvement in clinical outcomes in the former.⁴⁴ Subsequently, an international collaboration of intensivists and physicians launched the SSC, together with consensus guidelines, to direct the management of the septic patient.⁴⁰ The main aim of the bundle is to facilitate rapid implementation of key investigations and treatment.

Management of maternal sepsis in HICs is consistent. Pregnancy-specific sepsis bundles have been extrapolated from those developed for the general population, such as by the UK Sepsis Trust,⁴⁵ which takes into consideration physiological variables of pregnancy. The key elements emphasised are for clinicians to have a low index of suspicion to aid early recognition, perform essential investigations (cultures, blood lactate and hourly urine output) and to commence essential treatment (oxygen and intravenous fluids and antibiotics) – ‘the sepsis six’. In addition to promoting initiation of the bundle, the importance of critical care outreach involvement is emphasised (Table 4),^{1,2} as is engagement with relevant multidisciplinary specialities.

Although debate remains about the effect of bundles (between 2014 and 2015, three independent international, multicentre, randomised, controlled trials evaluating protocolised versus standard care demonstrated no benefit for patients with septic shock),^{46–48} improved clinical outcomes do appear to be associated with these measures. An SSC prospective cohort study showed a 25% relative risk decrease in mortality with application of the SSC bundle.⁴⁹ However, pregnancy-specific observational and interventional clinical trials are required.

[Heading 2] Management

The mainstay of management is supportive with a significant onus on early recognition of sepsis. Management consists of two key approaches: resuscitation and source control.⁴⁹

[Heading 3] Resuscitation

The SSC recommends initial intravenous fluid resuscitation at a rate of 30 ml/kg.⁴⁰ This recommendation is modified to 20 ml/kg by the RCOG,^{1,2} due to an increased risk of pulmonary oedema in pregnancy caused by decreased colloid oncotic pressure. This should be initiated immediately for the management of septic shock when there is a blood lactate of >4 mmol/l and/or to achieve a mean arterial pressure >65 mmHg.^{1–3}

Crystalloids are the primary choice of intravenous fluids, given the lack of evidence of overall benefit of crystalloids versus colloids and the renal toxicity associated with synthetic colloids (human albumin has not been shown to have this effect).⁵⁰

[Heading 3] Source control

Source control requires initiation of antibiotics. The SSC recommends combining only two classes of antibiotics for the treatment of septic shock.⁴⁰ However, in maternal sepsis, *Escherichia coli* (*E. coli*) and group B streptococcus are the most common bacterial pathogens, but the most severe outcomes are associated with *E. coli* and group A streptococcus.⁵¹ Therefore, the choice of antibiotic is guided by clinical assessment and the presumed site of infection. In reality, empirical antibiotics are started to cover Gram-positive, Gram-negative and anaerobic organisms, as per local microbial susceptibility patterns. De-escalation is then implemented in accordance with culture results.^{1,2}

In a number of cases, antibiotics alone are inadequate and abscess drainage or removal of infected material is required. Early efforts to identify less common sites of infection are key, as there are observational data to suggest that 28-day mortality rates increase considerably (from 26 to 42%) if there is a delay in source control.⁵⁰

[Heading 1] Controversies

Controversy surrounding the management of maternal sepsis starts at patient selection for implementation of the sepsis bundle.

The Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK (MMBRACE) collaboration's recommendations to recognise the ill patient promptly and commence treatment for those with suspected sepsis with fluids and antibiotics within 1 hour to improve outcomes has been extrapolated from the general population.^{10,40,45} As a result, many patients for whom the sepsis bundle has been initiated may not have an infectious aetiology. Fitzgerald et al.,⁵² in a prospective study of 175 intrapartum women with pyrexia >38°C, showed that no patients developed sepsis or required admission to ICU.⁵² They argue that de-escalation of antibiotics could be considered if sterile site cultures are negative at 48 hours and the patient is clinically well,⁵² along the lines of current national guidance for the neonate.⁵³ However, given the poor sensitivity/specificity of current microbiological culture techniques and in the absence of a more sensitive tool, de-escalation should be determined with microbiological guidance.

In labour, maternal pyrexia is associated with epidural analgesia, prolonged labour and the ambient temperature.⁵⁴ Maternal tachycardia may be the result of dehydration, the work of labour and, of course, critically but less commonly, underlying cardiorespiratory and metabolic/endocrine pathology. However, as chorioamnionitis is associated with an increased neonatal morbidity and mortality,⁵⁵ there is a low threshold to commence empirical broad-spectrum intravenous antibiotics, particularly during preterm labour at <34 weeks of gestation, as these neonates are at greatest risk of early-onset sepsis.⁵⁶

[Heading 2] Intensive care management

Maternal admissions to ICU for sepsis and septic shock are uncommon.⁵⁷ A number of ICU management strategies currently used without overwhelming support from clinical trials in obstetrics include glycaemic control, steroid use and novel vasoactive medicines. Their use is still debated among intensivists.

[Heading 3] Glycaemic control

Given the knowledge of increased glucose intolerance during pregnancy, the effects of tight glycaemic control during acute maternal illness are unknown. Conflicting results on the impact of tight glycaemic control versus standard care on ICU sepsis morbidity and mortality rates has prevented consensus for glucose monitoring. Currently, intensivists aim to ensure levels are less than 180 mg/dl (10 mmol/L).⁵⁰ This would be unlikely to adversely affect the baby; uncontrolled hyperglycaemia would be a greater threat.

[Heading 3] Steroids

Intravenous steroid use for the management of sepsis and septic shock in the general population has been a subject of controversy among intensivists for some time. A 2018 systematic review of 42 randomised clinical trials (RCTs) demonstrated a 2% reduction in 28-day mortality with steroids for patients admitted to the ICU.⁵⁸ However, the authors consider that there was a low quality of evidence to support this finding and state that the study recommendations are not applicable to the obstetric population.⁵⁸ Clinical judgement generally supports withholding intravenous hydrocortisone in the context of suspected maternal sepsis. Current RCOG guidelines do not consider steroid use for sepsis, but recommend cautious use in the context of promoting fetal lung

maturity.¹ Outside of sepsis, steroid use is generally advocated for maternal benefit, such as in severe asthma and connective tissue disease,^{59,60} but repeated steroid use may have a negative impact on the developing fetus, including a reduction in birthweight and head circumference. However, a recent Cochrane systematic review of studies in which both single and multiple courses of steroids were given demonstrated no increases in relative risk of low birthweight, but there was insufficient data to comment on the impact on neurodevelopmental delay and educational achievement.^{61,62} Furthermore, a large cluster randomised trial in six LMICs demonstrated an increase in neonatal mortality and risk of maternal infection with administration of antenatal steroids.⁶³

[Heading 3] Oxygen

Oxygen should be administered to achieve a saturation $\geq 94\%$,⁴⁵ and when patients are critically ill, a mixed venous oxygen saturation (SvO₂) of 65% or a ScvO₂ of 70% should be the target, as for the general population.^{1,2,40} In the third trimester of healthy pregnancy, the SvO₂ is approximately 80%, and currently there is limited evidence to guide the optimum SvO₂.⁶⁴

[Heading 3] Vasopressors

Vasopressors can be used for pregnant women admitted to ICU with septic shock. The first-line treatment in the general population is noradrenaline because of its efficacy. Catecholamines, notably dopamine, can cause arrhythmias and the addition of vasopressin can help to reduce catecholamine doses.⁵⁰ Reversible myocardial depression has been associated with sepsis, and inotropes can be considered when cardiac output has been compromised. Levosimendan is a relatively novel inotropic agent with vasodilator properties.⁶⁵ Interestingly, it also has anti-inflammatory and anti-oxidative effects,⁶⁶ which are potentially protective for sepsis-related tissue injury. Although small studies have demonstrated improved haemodynamic profiles and end-organ function when compared with dobutamine in patients with septic shock, a large UK multicentre, double-blind, RCT evaluating the addition of levosimendan to standard care did not demonstrate reduced mortality or end-organ dysfunction.⁶⁷ However, there are case reports of its use for the management of peripartum cardiomyopathy, when the addition of levosimendan to conventional treatment improved the left ventricular ejection fraction.^{68,69} Despite this, a small randomised trial of 24 pregnant women comparing adjunctive treatment with levosimendan versus conventional

care alone in cardiomyopathy showed no clinical improvement.⁷⁰ Currently, there is a lack of safety or efficacy evidence to recommend using this drug in obstetrics.⁷¹

[Heading 3] Intravenous immunoglobulins

Though rarely used in the obstetric population, intravenous immunoglobulins (IVIGs) can be considered as an adjunct to antibiotics, particularly during severe invasive staphylococcal and streptococcal sepsis.^{1,26} Dysregulated cytokine release during sepsis is associated with endothelial dysfunction that leads to hypotension, haemoconcentration, macromolecular extravasation and oedema. Immune regulation in sepsis is associated with improved outcomes.^{72,73} Here, IVIGs function by inhibiting harmful pro-inflammatory cytokine production (anti-tumour necrosis factor alpha and interleukins).

This advice is extrapolated from management of the general population. A Cochrane review demonstrated that IVIGs for adults with sepsis was associated with a reduction in mortality. Currently, there is little evidence of its benefit in treating sepsis during pregnancy.⁷⁵ A small, single-centre RCT appeared to show reduced morbidity and mortality following treatment with anti-endotoxin (as opposed to exotoxin) immunoglobulin therapy for obstetric and gynaecology patients with septic shock.⁷⁵

[Heading 3] Extracorporeal membranous oxygenation

Extracorporeal membranous oxygenation (ECMO) has been used for either cardiac or respiratory failure in a small number of patients in pregnancy and the puerperium, including as a consequence of severe sepsis and septic shock. The outcomes are generally good, with good recovery of cardiac function – the fetal survival rate is reported as 70% and the maternal rate is 80% (on a par with non-pregnant women).⁷⁶

[Heading 1] What the future holds

[Heading 2] Personalised medicine

In 2015, NHS England published their vision of the four Ps (prediction and prevention, precise diagnoses and targeted/personalised interventions) of personalised medicine forming an integral part of the future of healthcare in the UK.⁷⁷ Further research is required to determine how this can most effectively be applied to the diagnosis and management of maternal sepsis.

[Heading 3] Omics studies: biomarkers for the obstetric patient

Omics-based technologies enable quantitative and qualitative analysis of the molecules involved in biological pathways, including genes or metabolites, to help elicit the pathophysiology of a given disease process. Sepsis research using omics technologies aims to identify host and pathogen targets as biomarkers, as well as potential avenues to modulate biological processes using novel therapies. A comprehensive and interesting overview of this exciting area of research by Horgan et al. can be read in a prior issue of *The Obstetrician & Gynaecologist*.⁷⁸

[Heading 1] Ethical considerations

Omic technologies for precision medicine have the capacity to transform health care in terms of diagnosis and treatment. The cost of developing these is high, which limits their availability in LMICs, where the disease burden is high. Global communities are starting to facilitate access to LMICs. For example, the Genomic Medicine Alliance aims to foster collaborations in genomics research between developing and developed countries.⁷⁹ Other initiatives include the Human Heredity and Health in Africa initiative, which is developing research into the genetic and environmental basis of non-communicable and infectious diseases across 30 African countries, and the African Centre of Excellence for Genomics of Infectious Diseases, which in 2014 demonstrated patterns of viral evolution and transmission of the Ebola virus in West Africa through genomic sequencing.^{80–82}

[Heading 1] Conclusion

The evidence on which we base our practice in managing sepsis is evolving rapidly. Largely population based in the past, a shift to an individualised approach to clinical care using precision medicine is being embraced to tackle the heterogeneity of the disease phenotype. We know pregnancy presents a unique physiological picture, which will result in unique responses to disease processes. Recognising these responses and modifying the diagnostic approach is essential. Translational research and clinical trials in pregnancy and the puerperium may allow quicker gains in understanding the pathogenesis of sepsis in pregnancy and the puerperium.

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[Figure legends]

Figure 1. Pathophysiology of sepsis. The pathophysiology of sepsis is complex and involves the interaction of multiple biological pathways via positive and negative feedback loops. When communication between these pathways becomes uncontrolled, widespread tissue injury can lead to organ dysfunction and sepsis. On breaching the tissue epithelium/mucosal barrier, pathogens are first identified for clearance by immune cells of the innate system, monocytes and neutrophils. Invading pathogens have conserved surface molecular regions that act as danger signals (pathogen associated molecular patterns [PAMPs]) which are recognised by monocyte pathogen recognition receptors (PRRs) such as the toll-like receptor 4 (TLR-4). Interaction between the two triggers monocyte intracellular gene transcription of pro-inflammatory intracellular cytokines and chemokines via NF κ B; resulting in recruitment of more immune cells to the site of infection and activation of inducible nitric oxide synthase (iNOS), which causes nitric oxide overproduction that functions to aid pathogen clearance but is also a potent vasodilator contributing to systemic hypotension and attenuated cardiac function. Neutrophils clear bacteria by phagocytosis or enzymatic degradation, which may cause tissue injury. This releases danger associated molecular patterns (DAMPs) such as heat shock protein (hsp) or high-mobility group box-1 (HMGB-1) which can result in rapid escalation of cell recruitment, cytokine release and tissue injury. Cells of the adaptive system, T cell and B cells, can recognise specific bacterial associated antigens. T cells target the pathogen via cytotoxic activity (CD8) or by the production of cytokines (CD4). Adaptive responses from T regulatory cells and other immune suppressive leukocytes, in turn, produce immuno-modulatory molecules (IL-10, TGF- β) during the contraction phase of the immune response, alongside T-helper CD4 production of anti-inflammatory cytokines (IL-4). B cells produce antigen specific antibodies which opsonise to pathogens with complement to facilitate neutrophil phagocytosis. Pathogens can trigger the complement cascade which, in turn, can activate the coagulation system. In severe sepsis this is associated with disseminated intravascular coagulation (DIC), a mixed clinical picture of microthrombus formation and haemorrhage. Adapted with permission from the text of Conway-Morris et al.¹²

Figure 2. The pathophysiology of septic shock. Interaction between a PAMP on bacteria and the pathogen recognition receptor on innate cells triggers release of nitric oxide and cytokines. Nitric oxide is associated with reduced vascular tone and vasodilatation. When this is severe, hypotension and septic shock occurs. Cytokine release causes tissue injury and release of DAMPS. These can cause recruitment of more innate cells and can cause tissue injury e.g., of the heart. Cardiomyocyte death may lead to reversible reduced cardiac function. Adapted from Kakihana et al.¹³ PRR = pattern

recognition receptor; PAMP = pathogen associated molecular pattern; DAMP = danger associated molecular pattern.

Figure 3. The effects of pregnancy physiology on the clinical presentation of sepsis. Adapted from Joseph et al.¹⁶

Table 1. Obstetrically modified SOFA score, demonstrating a sepsis-related scoring system that uses pregnancy-specific physiological variables in order to identify the critically ill obstetric patient

System parameter	Score		
	0	1	2
Respiration			
PaO ₂ /FiO ₂	≥400	300 to <400	<300
Coagulation			
Platelets (× 10 ⁶ /l)	≥150	100–150	<100
Liver			
Bilirubin (μmol/l)	≤20	20–32	>32
Cardiovascular			
Mean arterial pressure (mmHg)	≥70	<70	Vasopressors required
Central nervous system	Alert	Rousable by voice	Rousable by pain
Renal			
Creatinine (μmol/l)	≤90	91–120	>120

Adapted with permission from the Society of Obstetric Medicine Australia and New Zealand guidelines for the investigation and management of sepsis in pregnancy.²⁶ PaO₂ = partial pressure of oxygen (in mmHg, millimetres of mercury); FiO₂ = fraction of inspired oxygen (expressed as a decimal); SOFA = Sequential (sepsis-related) Organ Failure Assessment.

Table 2. Obstetrically modified qSOFA score, allowing a rapid clinical assessment before investigations are available in order to identify the critically ill obstetric patient

Parameter	Score	
	0	1
Systolic blood pressure (mmHg)	≥90	<90
Respiratory rate	<25 breaths/minute	≥25 breaths/minutes
Altered mentation	Alert	Not alert

A score ≥2 is associated with an increased risk of mortality. Adapted with permission from the Society of Obstetric Medicine Australia and New Zealand guidelines for the investigation and management of sepsis in pregnancy.²⁶ qSOFA = quick Sequential (sepsis-related) Organ Failure Assessment; mmHg = millimetres of mercury).

Table 3. The Sepsis in Obstetrics Score (SOS): a model to identify risk of morbidity from sepsis in pregnancy

Variable	Value								
Score	+4	+3	+2	+1	0 (normal)	+1	+2	+3	+4
Temp (°C)	>40.9	39– 40.9		38.5– 38.9	36–38.4	34– 35.9	32– 33.9	30– 31.9	<30
SBP (mmHg)					>90		70– 90		<70
HR (bpm)	>179	150– 179	130– 149	120– 129	≤119				
RR (breaths/minute)	>49	35–49		25–34	12–24	10– 11	6–9		≤5
SpO ₂ (%)					≥92	90– 91		85– 89	<85
Leucocytes (number/μl)	>39.9		25– 39.9	17– 24.9	5.7– 16.9	3–5.6	1–2.9		<1
Immature neutrophils (%)			≥10%		<10%				
Lactic acid (mmol/l)			≥4		<4				

This table uses a composite of physiological variables of pregnancy and biomarkers to identify pregnant women with an increased risk of morbidity in association with suspected sepsis. Patients with a SOS score ≥6 are more likely to be admitted to intensive care. Adapted with permission from Albright et al. (2014).³³ SBP = systolic blood pressure in mmHg (millimetres of mercury); HR = heart rate; bpm = beats per minute RR = respiratory rate.

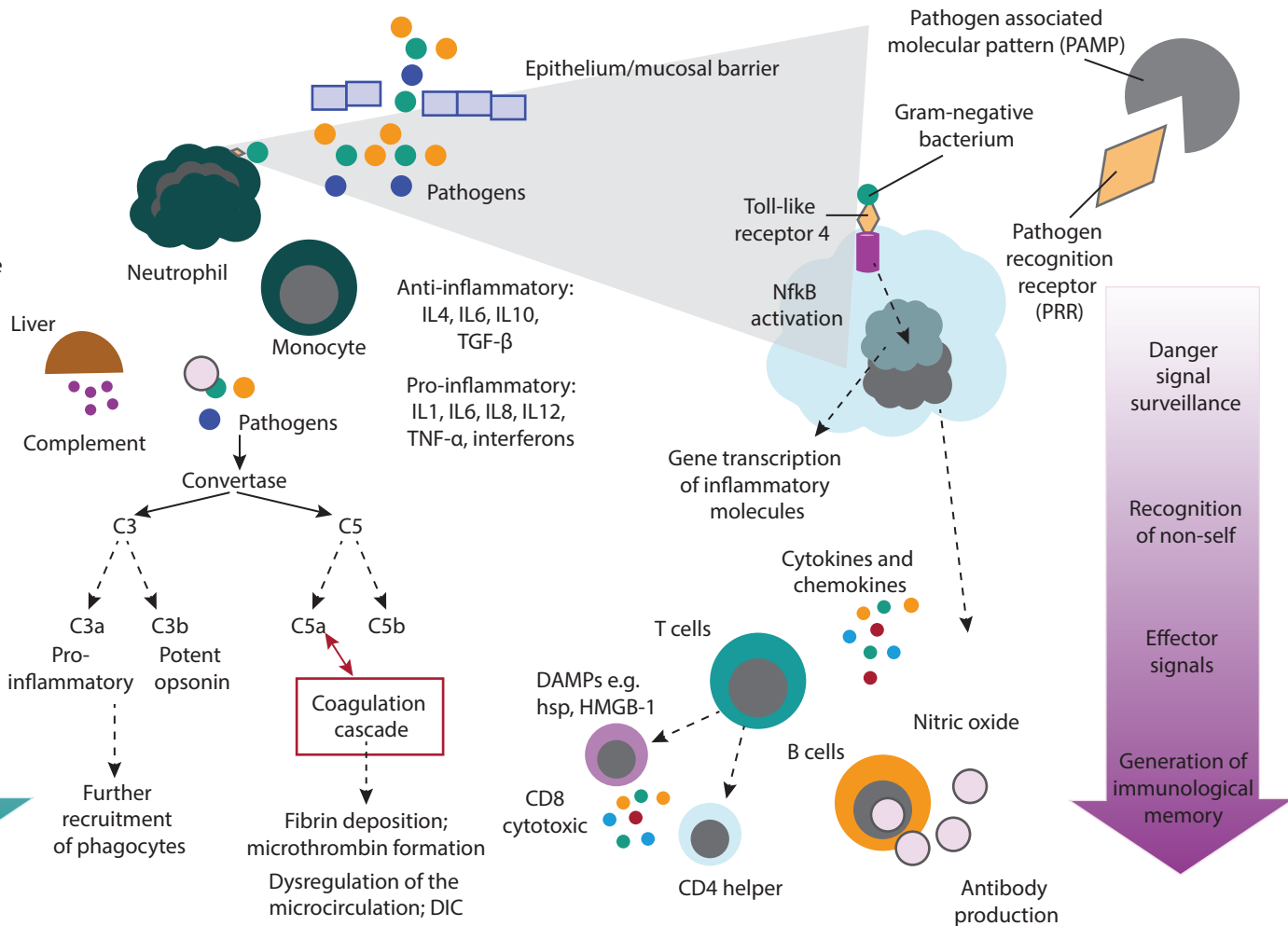
Table 4. Indications for transfer to the intensive care unit

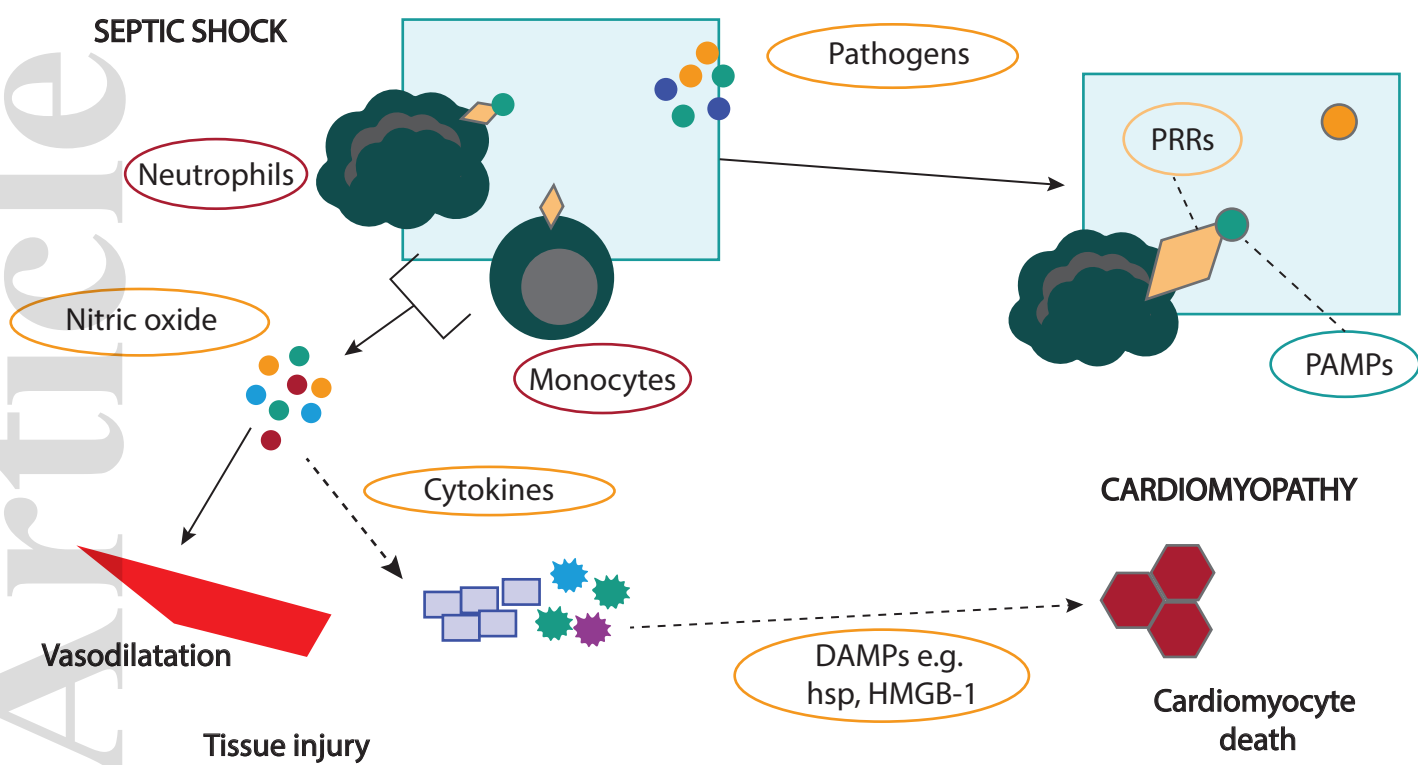
System	Indication
Cardiovascular	Hypotension or raised serum lactate persisting despite fluid resuscitation, suggesting the need for inotrope support
Respiratory	Pulmonary oedema Mechanical ventilation Airway protection
Renal	Renal dialysis
Neurological	Significantly decreased conscious level
Miscellaneous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

Adapted with permission from the Royal College of Obstetricians and Gynaecologists.^{1,2}

Levels of defence

Innate immune
Adaptive immune
Complement system
Coagulation cascade





Pregnancy

Cardiovascular:

- ↓ Systemic vascular resistance (25–30%)
- ↓ Blood pressure
- ↑ Blood volume (40–50%)
- ↑ Heart rate (10–20 bpm)
- ↑ Cardiac output (40%)
- Aorto-caval compression

Respiratory:

- ↓ Pulmonary vascular resistance and plasma colloid pressure
- ↓ Residual volume
- ↑ Functional residual capacity
- ↑ Tidal volume
- ↑ Minute ventilation
- Compensated respiratory alkalosis

Renal:

- ↑ Renal plasma flow
- ↑ Glomerular filtration rate
- Renal collecting system dilatation

Coagulation

- ↑ Factors I, II, VII, VIII, IX, XII
- ↑ (x5) plasminogen activator inhibitors (PAI) I & II
- ↓ Protein S
- ↔ Anti-thrombin and Protein C



Sepsis

Cardiovascular:

- ↓ Systemic vascular resistance
- ↓ Blood pressure
- ↑ Heart rate
- Vasodilatation
- Myocardial depression

Respiratory:

- ↑ Pulmonary microvascular pressure and permeability
- Acute lung injury

Renal:

- Ischaemia
- Vasoconstriction
- Cytokine-mediated renal cell injury

Coagulation

- ↑ Procoagulant effects
- ↑ Thrombin production
- ↓ Activated Protein C
- Fibrinolysis (increased PAI II)

Cumulative effect

Cardiovascular	Respiratory	Renal	Coagulation
Rapid haemodynamic collapse	• Susceptibility to pulmonary oedema • Rapid decrease in oxygenation • Adult respiratory distress syndrome • Decreased ability to compensate for metabolic acidosis	Acute kidney injury	• Increased microvascular thrombus formation • Microcirculation dysregulation • Tissue hypoperfusion • End-organ dysfunction