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RCOG GREEN-TOP GUIDELINE

Identification and Management of Maternal Sepsis During and Following Pregnancy

Green-top Guideline No. 64

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KEY RECOMMENDATIONS

- Consider sepsis as a possible diagnosis in all women during pregnancy, and in the intrapartum and postpartum period, with a suspected infection and whose clinical condition rapidly deteriorates. [Good Practice Point (GPP)]
- If sepsis is suspected in the community, urgent escalation and referral to hospital is indicated. [GPP]
- Monitoring of a woman with suspected sepsis should be performed using an early warning system modified for obstetrics, managed through a multidisciplinary approach with early escalation and senior input. [GPP]
- Serum lactate should be measured urgently in women with features indicating a high risk of sepsis. Serum lactate of 4 mmol/l or more should prompt immediate escalation of care, including consideration of discussion with critical care team. [Grade D]
- Any relevant imaging studies should be performed promptly to confirm the source of infection. [Grade D]
- Use of a sepsis bundle may improve compliance with urgent management in women at high risk of sepsis. [Grade D]
- Administration of intravenous broad-spectrum antibiotics is recommended within one hour in women at high risk of sepsis, with or without septic shock. [Grade C]
- In a critically ill pregnant woman, birth of the baby can be expedited if it would be beneficial to the woman or the baby or to both. A decision on the timing and mode of birth should be made by a senior obstetrician following discussion with the woman and/or family if her condition permits. [GPP]
- During the intrapartum period, continuous electronic fetal monitoring is recommended. Caution is required if considering fetal blood sampling. [GPP]
- An individual risk assessment should be made by a senior anaesthetist with regards to type of anaesthesia, as well as the need for invasive monitoring. [GPP]
- Babies of women treated for sepsis during labour, or in the 24 hour period before or after birth, require assessment for risk factors and clinical indicators of neonatal infection. [Grade D]

This is the second edition of this guideline, which was first published in 2012 as two separate guidelines: Green-top Guideline (GTG) No. 64a *Bacterial Sepsis in Pregnancy*; and GTG No. 64b *Bacterial Sepsis Following Pregnancy.*

- If either the woman or the baby is infected with invasive Group A beta-haemolytic streptococcus (iGAS) disease in the postpartum period, both should be treated with antibiotics and full infection control precautions adopted, including barrier nursing as per local guidelines. [GPP]
- Herpes simplex sepsis is a rare but potentially fatal disease if contracted in the peripartum period and more needs to be done to raise awareness of it as a potential diagnosis to exclude in sepsis pathways and for early consideration of the use of aciclovir. [GPP]

1 | Purpose and Scope

The need for such a guideline was originally identified by the 2007 Confidential Enquiry into Maternal Deaths [1]. The scope of this guideline covers the recognition and management of sepsis in the antenatal, intrapartum and postpartum periods, including post-abortion sepsis. The scope includes bacterial infections arising in the genital tract or elsewhere and influenza and their management in secondary care. Sepsis arising due to primary viral (other than influenza and HSV) or parasitic infection is outside the scope of this guideline. There is separate specific guidance available on Coronavirus (COVID-19) infection in pregnancy [2].

This guideline is for healthcare professionals who care for women, non-binary and trans people suspected of, or diagnosed with, sepsis in primary or secondary healthcare. This guideline excludes mild to moderate illness in primary care.

Within this document we use the terms woman and women's health. However, it is important to acknowledge that it is not only women for whom it is necessary to access women's health and reproductive services in order to maintain their gynaecological health and reproductive wellbeing. Gynaecological and obstetric services and delivery of care must therefore be appropriate, inclusive and sensitive to the needs of those individuals whose gender identity does not align with the sex they were assigned at birth.

2 | Introduction and Background

Sepsis during and following pregnancy remains an important cause of maternal death globally, accounting for 11% of all maternal deaths [3]. Between 2019–21, 241 of 2 066 997 women giving birth in the UK died. Of these, 78 women died of sepsis, either direct or indirect. Despite a statistically non-significant increase in the overall maternal death rate due to sepsis in the UK between 2016–18 and 2019–21, most of this was accounted for by SARS-COV-2 viral infections in unvaccinated women.

TABLE 1 | Definitions for acronyms.

CPE	Carbapenemase producing enterobacterales
GAS	Group A beta-haemolytic Streptococcus
MBRRACE	Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries
MSSA	Methicillin Sensitive *Staphylococcus Aureus*
MRSA	Methicillin Resistant *Staphylococcus Aureus*
SARS-CoV-2	Severe acute respiratory syndrome-related coronavirus
VRE	Vancomycin resistant Enterococcus

In the UK and Ireland, during or up to six weeks after the end of pregnancy and defined "*in the broadest sense as death from a primary infective cause*" the overall mortality rate for sepsis was 2.50 per 100 000 maternities (95% CI 1.89–3.25 per 100 000) [1, 4].

Between 2019–21, 10% of all maternal deaths were due to sepsis and 14% of deaths were due to COVID-19 infection [4]. Overall, 47 of the 78 deaths (60%) were attributable to viral infections, 43 due to COVID-19, one varicella zoster virus, one viral myocarditis of unknown cause and two following influenza A [4]. Deaths attributable to influenza A were significantly lower than in the years 2010–12 when 13 women died, reflecting the importance of vaccination. Only one of the 43 women who died from SARS-CoV-2 had been vaccinated, and had only had one dose of COVID-19 vaccine [4].

The number of bacterial sepsis related deaths was significantly higher than in the previous MBRRACE report (2015–2017), [5] where a breakdown of responsible agents was given as 27 deaths overall, 16 classified as 'direct' maternal deaths from sepsis and ten due to genital tract sepsis [5]. Excluding SARS-COV-2 deaths, the dramatic decline from an overall figure of 2.04 deaths due to sepsis per 100 000 maternities (data from the 2009–12 MBRRACE report) [6] likely reflects the combination of increasing influenza vaccine uptake, mandatory education of healthcare staff to recognise sepsis and implementation of various sepsis-related guidelines, including the previous edition of this RCOG Green-top Guideline. The National Maternity and Perinatal Audit (NMPA) report examining maternity admissions to intensive care in 2015/2016 highlighted the importance of infection as the second most common cause for admission, after haemorrhage. The most common infections were pneumonia (44%), urinary tract (20.4%) and genital tract infections (18.5%) [7].

Suboptimal care continues to be identified in many cases where women die from sepsis [1, 3, 4]. To reduce maternal death from sepsis requires high levels of vigilance and to "*Think Sepsis*" at an early stage with any unwell, pregnant or recently pregnant woman. Key actions are the importance of early diagnosis, the rapid initiation of broad spectrum antibiotics and the need for review by senior doctors and midwives and early involvement of relevant experts such as infection specialists and critical care, where appropriate. To avoid preventable deaths the importance of maternal vaccination for influenza and COVID-19 must be continually promoted [2, 4, 5].

Not included in the 2023 MBRRACE report are two women who died of disseminated Herpes Simplex virus (HSV) infection

following birth by caesarean section, a very rare cause of sepsis. These cases prompted calls for HSV and other viral infections to be considered when evaluating the cause of postpartum infection, [8] as specified by the Coroner's prevention of future death report on the cases [9].

3 | Identification and Assessment of Evidence

This RCOG guideline was developed in accordance with standard methodology for producing RCOG Green-top Guidelines [10]. The Cochrane Library and electronic databases (DARE, EMBASE, Trip, MEDLINE and PubMed) were searched using the relevant Medical Subject Headings (MeSH) terms, including all subheadings and synonyms, and this was combined with a keyword search. Search terms included 'sepsis and pregnancy', 'bacterial infection and pregnancy', 'antenatal bacterial infection', 'bacterial sepsis', 'intrapartum septic shock', 'intrapartum infection' and 'maternal pyrexia' and the search was limited to humans and English language. The search was restricted to articles published between September 2011 to October 2023.

Where possible, recommendations are based on available evidence. In the absence of published evidence, these have been annotated as 'good practice points'. Further information about the assessment of evidence and the grading of recommendations may be found in Appendix 1.

4 | Understanding Maternal Sepsis

4.1 | What is Maternal Sepsis?

In 2017 the World Health Organisation defined maternal sepsis as *"a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or postpartum period."* [11] This definition is aligned with the current international consensus definition of adult sepsis and supersedes the prior use of the term sepsis to describe infection that has caused a systemic inflammatory response (SIRS) [11].

Aligning the definition of maternal sepsis with the definition used in the wider adult population is important for consistency in care across patient groups and to enable direct comparisons. This also reduces the challenge caused by the physiological changes arising from the pregnancy itself, which make it difficult to apply the SIRS criteria during pregnancy. The international consensus statement defines organ dysfunction as an increase in the sequential organ failure assessment (SOFA) score of more than two points. This makes the formal diagnosis of sepsis a retrospective one, as the calculation of the SOFA score requires laboratory investigations to be completed (See Appendix 2).

Septic shock is now described as a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain an adequate blood pressure (MAP 65 mm Hg or more), alongside a persistent serum lactate (either venous or arterial) level more than 2 mmol/L despite adequate volume resuscitation. Using these criteria, hospital mortality is in excess of 40%. There are no widely agreed pregnancy specific adaptations to this definition [12].

4.2 | Which Women are at Risk of Sepsis?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
All women are at risk of sepsis during pregnancy and the postpartum period.	**4**	**GPP**	Sepsis is a recognised complication of labour and birth.
During pregnancy and the postpartum period clinicians should be aware of and be able to recognise the risk factors for developing maternal sepsis.	**4**	**GPP**	Sepsis is an important cause of maternal morbidity and mortality.
Women at risk of sepsis in pregnancy should be made aware of this and provided information including access to care to reduce risk.	**4**	**GPP**	Sepsis is an important cause of maternal morbidity and mortality.

Multiple risk factors for maternal sepsis are described in the literature and in maternal morbidity and mortality reports (Table 1). Pregnant women are at 20 times increased risk of invasive Group A beta-haemolytic Streptococcus (iGAS) infection compared with non-pregnant women, [13] and are at an 80-fold increased risk up to 28 days postpartum [14].

4.3 | What are the Common Organisms Causing Sepsis?

Maternal sepsis is caused by a wide range of organisms (Table 2). The emergence of *Escherichia coli (E. coli)* and beta-haemolytic streptococci of Lancefield group A (GAS) as important causes of sepsis and death in pregnant women has been highlighted by several authors [13, 14, 17–20]. In one series, 13 of 45 (29%) women with iGAS infections were admitted to intensive care, and two died [20].

Morbidity due to iGAS remains significant, however, it has fallen to less than one third of that reported in the early Centre for Maternal and Child Enquiries (CMACE) report that initially recommended specific education on sepsis for maternity staff [22]. During 2019–2021, six women (accounting for 7.6% of the sepsis attributable deaths) died of GAS [4].

Pregnancy associated GBS sepsis remains an important cause of maternal sepsis [21, 23, 24, 25] and, although morbidity with GBS is more common than that of iGAS, there were no GBS related maternal deaths during 2019–21 [4]. *[Evidence level 3]*

Co-infections with mixtures of Gram-positive and Gram-negative organisms remain common, especially in chorioamnionitis. Coliform infection is particularly associated with urinary sepsis, preterm premature rupture of membranes (PPROM) and cerclage [15, 26, 27]. Anaerobes, usually *Peptostreptococcus spp* and *Bacteroides spp* in mixed infections, account for some 8.3% of the organisms causing maternal sepsis, especially assoiciated with chorioamnonitis [21]. *[Evidence level 3]*

Methicillin-resistant *Staphylococcus aureus* (MRSA) infection in pregnancy was reported in 1.9% of North American women [28]. Since routine antenatal MRSA screening is no longer conducted in the UK, the current prevalence in pregnancy is unknown,

TABLE 1 | Risk factors for developing maternal sepsis during pregnancy/postpartum [15–19].

Maternal	Obstetric
• Obesity • Diabetes in pregnancy • Iron deficiency anaemia • Maternal age > 35 years • Impaired immunity/Immunosuppressant medication • Women of ethnic minority • Renal/Cardiac/Liver disease • History of pelvic infection • Contact with iGAS [13, 14, 17, 18] • Intravenous drug use [19]	• Prolonged rupture of membranes • Caesarean birth • Vaginal trauma • Retained pregnancy tissue • Amniocentesis and other invasive procedures • Multiple gestation • Cervical cerclage

Note: iGAS, invasive Group A beta-haemolytic Streptococcus.

but is probably below 1%, in line with other European contries [29]. In 2010, 0.5% of pregnant women screened in Birmingham were MRSA positive [30]. Panton Valentine Leukocidin (PVL)-producing MRSA was responsible for maternity outbreaks in Ireland in 2021 [31] and London in 2021–22 [32]. Vertical transmission of MRSA at birth due to vaginal colonisation occurs in 13% of neonates born to carrier mothers [33]. PVL-producing staphylococci are particularly associated with mastitis and breast abscesses [32, 34, 35]. PVL-related maternal deaths have been reported rarely, and more likely to occur with unexpected MRSA producing PVL [1]. The true prevalence of PVL-producing staphylococci in pregnancy in the UK is unknown since few laboratories test for PVL production. *[Evidence level 3]*

Gram negative producing extended-spectrum beta-lactamases (ESBL) [36] are increasingly carried by UK residents and foreign travellers. Carbapenemase producing *Enterobacteraceae* (CPE) are increasing worldwide and pregnant women who are gut [36–38] or vaginal [39] carriers may pass these organisms to the baby [40]. Since ESBLs render most cephalosporins ineffective and CPEs render carbapenems ineffective, their presence means empirical choices for mildly penicillin-allergic patients (simple rash) are ineffective. *[Evidence level 3]*

4.4 | What are the Likely Causes of Sepsis Outside the Genital Tract and how Might They be Identified?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
A thorough history is recommended as soon as possible after presentation and an appropriate physical examination should be offered.	**4**	**GPP**	This is considered best practice.
Consider and investigate other non-infective causes that can masquerade as sepsis.	**4**	**GPP**	Other obstetric and non-obstetric conditions share features with the presentation of sepsis and must be considered.

With increased awareness and earlier, more effective therapy, the reported incidence of pregnancy associated GAS has fallen [4]. GAS was the cause of five maternal deaths (11%) during the 2019–21 period [4]. Pregnancy-associated GBS sepsis remains more common than GAS [23–25], but the rate of neonatal GBS sepsis continues to fall, [41] and no women died of GBS sepsis in the UK during 2019–2022 [4].

TABLE 2 | Organisms causing septicaemia in 276 cases of pregnancy -related sepsis in Ireland [21].

Organism	% of positive blood cultures
Escherichia coli	37.3%
Group B beta-haemolytic streptococcus (GBS)	20.6%
Anaerobes	8.3%
Staphylococcus aureus	7.6%
Group A beta-haemolytic streptococcus (GAS)	4.3% (10/12 women were post-partum)
Coliforms other than *Escherichia coli*	4.2%
Haemophilus influenzae	1.4%
Listeria monocytogenes	0.7%

The first point of contact with a woman may not be face to face, and careful assessment should be encouraged via telephone triage and community assessment. However, *"repeated presentation to the general practitioner or community midwife or repeated self-referral to the obstetric triage or day assessment unit should be considered a 'red flag'"* [4] and warrants a thorough clinical assessment to investigate for signs of sepsis (see Table 5 and Appendix 3). Therefore, women with infection should be offered early in-person assessment [4] and those with red-flag features seen urgently in a setting where appropriate treatment can be rapidly initiated. Other diseases can masquerade as sepsis, such as pre-eclampsia or other rare diseases (e.g. thrombotic thombocytopenic purpura, haemophagocytic lymphohistiocytosis). *[Evidence level 4]*

Table 3 lists the common sites of sepsis and how these may be identified; Table 4 lists conditions that may masquerade as sepsis.

5 | Recognising Maternal Sepsis

5.1 | What Should Prompt Recognition of Sepsis?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Consider sepsis as a possible diagnosis in all women during pregnancy, and in the postpartum period, with a suspected infection and whose clinical condition rapidly deteriorates.	**4**	**GPP**	The diagnosis of sepsis can be challenging during and after pregnancy and should be considered in the unwell pregnant woman

TABLE 3 | Potential sites of sepsis outside the genital tract and clinical features of their presentation.

Site	Diseases	Clinical features
Head	Meningitis Meningoencephalitis	Photophobia, neck stiffness Altered conscious level, delirium, focal neurology seizures
Ear Nose Throat	Otitis Media Sinusitis Pharyngitis/Laryngitis	Ear ache, muffled hearing Purulent nasal discharge, facial pain, headache Sore throat, cervical lymphadenopathy Hoarse voice
Chest	Pneumonia (viral & bacterial)	Cough with sputum is more likely bacterial Hypoxia, pleuritic pain
Cardiac	Infective endocarditis	Regurgitant murmur, embolic lesions Splinter haemorrhages and Janeway lesions
Hepatobiliary	Cholecystitis/Cholangitis Pancreatitis	Right upper quadrant pain, Murphy sign positive for cholecystitis Upper abdomen pain, radiating to back
Abdomen	Gastroenteritis Appendicitis Bowel perforation (more common in inflammatory bowel disease)	Diarrhoea and vomiting McBurney's sign for appendicitis, atypical presentations common in pregnancy Acute abdomen
Breast	Mastitis may lead to breast abscesses, [32, 34] necrotising fasciitis [42], toxic shock syndromes [43, 44]	Inflamed breast, pain, features of sepsis and 'bruising' suggests deeper infection such as necrotizing fasciitis [42, 45]
Urinary Tract	Urinary Tract Infection Pyelonephritis Covert Genital Herpes	Dysuria Loin pain, back pain Haematuria Acute urinary retention
Regional anaesthetic blockade related infection	Meningitis Spinal abscess	Headache, photophobia Back pain Focal neurology Permanent spinal cord or cauda equina damage may result if neural compression is not relieved urgently
Wound infection	Peripheral cannula thrombophlebitis Caesarean birth or episiotomy wounds	Skin and soft-tissue infections are particularly associated with early toxic shock syndromes [41, 44] (rash and conjunctival redness)
Necrotising fasciitis	Early necrotising fasciitis (deep in tissues)	Cardinal feature is of agonising pain, typically necessitating increasing amounts of analgesia culminating in opioids, there may be no skin changes early on Later, ascending infection to the skin, producing blisters and frank necrosis [42, 45]

Healthcare professionals should assess all women with suspected infection for maternal sepsis with a risk stratification tool; an example of a sepsis risk stratification tool is given in Appendix 3. The possibility of COVID-19 must also be considered, and an assessment for possible COVID-19 conducted in line with current recommendations [2]. Health care providers should be aware of the red flag symptoms and signs of maternal sepsis and of the rapid, potentially lethal course of sepsis and septic shock (Table 5). Disease progression may be much more rapid than in the non-pregnant state. Signs of infection, including pyrexia, may not always be present and are not necessarily related to the severity of sepsis. Genital tract sepsis may present with constant severe abdominal pain and tenderness not relieved by usual analgesia. Severe infection may be associated with preterm labour. Toxic shock syndrome (TSS), caused by staphylococcal or streptococcal exotoxins, can produce generalised symptoms including nausea,

TABLE 4 | Non-infective causes that can masquerade as sepsis.

Disease	Shared clinical features with sepsis
Blood transfusion reaction	Pyrexia, rash
Autoimmune disease	Pyrexia
Acute fatty liver of pregnancy	Pyrexia
Disseminated malignancy	Pyrexia
Thrombotic thombocytopenic purpura	Pyrexia, acute renal failure, altered consciousness, thrombocytopenia
Haemophagocytic lymphohistiocytosis	Pyrexia, pancytopenia, lymphadenopathy, rash
Occult bleeding	Hypothermia, raised lactate, shock
Epidural related maternal fever	Pyrexia
Misoprostol side-effect	Pyrexia

vomiting and diarrhoea [41, 44]. Severe pain, out of proportion to clinical signs, suggests necrotising fasciitis (NF) [42, 45]. Blisters developing on a background of inflammation or a watery vaginal discharge suggests haemolytic streptococcal infection. A 'sunburn' rash and conjunctival suffusion suggests early TSS (i.e. due to *S. aureus*), whereas the rash is only present in 50% of streptococcal toxic shock [46]. Mastitis can occur in the antenatal period as well as postnatally. *[Evidence level 4]*

Occasionally viral infections can present with sepsis, e.g. influenza, [49] SARS-COV-2 and disseminated HSV [50, 51]. HSV is a rare and potentially fatal disease if contracted in the peripartum period. While it can present with encephalitis, or rarely febrile hepatitis, in many cases there are no obvious clinical signs of disseminated herpetic infection which can differentiate it from a bacterial cause of sepsis [50]. Pregnancy is a risk factor for HSV hepatitis, which is responsible for 2%–4% of all acute hepatitides [50]. The sicker the woman is with disseminated HSV infection (in the absence of rash), the more likely the incorrect diagnosis of Hemolysis, Elevated Liver enzymes

TABLE 5 | Clinical symptoms, signs and risk factors suggestive of sepsis during pregnancy/postpartum [47].

Red Flags or features in patients with suspected sepsis that indicate high risk of sepsis (recommend immediate management either with initiation of a sepsis bundle for inpatients or referral by blue light transfer from the community)	
Objective evidence of altered mental state	GCS < 15 or 'not alert' in AVPU classification
Respiratory rate	≥ 25 breaths/min
Oxygen saturation	< 94% on room air*
Heart rate	> 130 bpm
Blood pressure	Systolic < 90 mmHg
Urine output	Not passed urine in > 12 hours or if catheterised < 0.5 ml/kg urine per hour
Amber flags or features in patients with suspected sepsis that indicate moderate risk of sepsis (this warrants senior clinical review within 1 hour for inpatients or as soon as possible in the community)	
Behavioural/mental status change	
Acute deterioration in functional ability	
Respiratory rate	21–24 breaths/minute
Heart rate	100–130 beats/minute or new dysrhythmia
Systolic BP	91–100 mmHg
Urine output	Not passed urine in last 12 hours or if catheterised 0.5–1 ml/kg urine per hour
Has had invasive procedure in last 6 weeks (e.g. caesarean birth, assisted vaginal birth, surgical management of miscarriage, cerclage, CVS, amniocentesis, miscarriage, termination)	
Impaired immune system (illness or medication, including oral steroids)	
Temperature	< 36°C or > 38°C*
Current diabetes or gestational diabetes	
Close contact with GAS (e.g. scarlet fever, tonsillitis, iGAS)	Prolonged close contact with the case in a household type setting during the seven days before the onset of illness [17]
Prolonged rupture of membranes	18–24 hours
Prolonged vaginal bleeding and abdominal pain post birth [4]	
Offensive vaginal discharge	

AVPU: Alert, vocal, pain, unresponsive; CVS, chorionic villus samlping; GAS, Group A beta-haemolytic streptococcus; iGAS, invasive Group A beta-haemolytic streptococcus. *These features were not included in the NICE Guideline (NG51) sepsis risk stratification approach, but are present in many maternity specific screening and decision tools, and have therefore been included here for completeness [48].

and Low Platelets (HELLP) syndrome or acute fatty liver of pregnancy [51]. *[Evidence level 4]*

Disseminated HSV infection, presenting with sepsis, encephalitis or hepatitis, is rare but often fatal if contracted in the peripartum period. As there are often no clinical signs of disseminated herpetic infection which can differentiate it from bacterial causes of infection, HSV should be considered as a causative agent in women where there is a failure of first-line antibacterial medication. Early intravenous aciclovir therapy is vital, and should ideally be started at the same time as the first change in antibacterial regime. The diagnosis should be considered if a pregnant woman presents with acute febrile hepatitis, as evidenced by markedly (greater than 10 times) raised ALT with normal bilirubin, encephalitis or disseminated, often vesicular skin lesions, or a combination of these [50, 51]. *[Evidence level 4]*

Women of Black, Asian and minority ethnic background are at higher risk of developing sepsis. This highlights the clear need to develop culturally relevant maternity services, to meet the growing needs of pregnant women from Black, Asian and minority ethnic backgrounds in the UK, and reduce the persistent health inequalities to improve maternal and infant outcomes [52, 53]. Healthcare providers must be aware of this increased risk in ethnic minority groups and recognise that important signs of sepsis, such as skin rashes, may present differently [48]. *[Evidence level 2–]*

Non-response of symptoms to treatment for other causes of serious illness, e.g. treatment of haemorrhage, or deterioration should prompt a re-consideration of sepsis as a concurrent or alternative diagnosis.

5.2 | What are the Appropriate Triggers or Features of Sepsis that should Prompt hospital Admission from the Community?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
If sepsis is suspected in the community, urgent escalation and referral to hospital is indicated.	**4**	**GPP**	Sepsis is a medical emergency requiring hospital based care.

Signs and symptoms of possible sepsis should prompt urgent referral for hospital assessment; if a woman appears seriously unwell, referral for hospital assessment should happen by emergency ambulance services. Screening and decision tools suitable for community use are available and may assist with appropriate management [12]. The 2023 MBBRACE report recommended *"post delivery, streptococcal infection, particularly GAS, is most likely to present within 12 hours post-birth. Infection should be suspected and actively ruled out for women who have recently given birth and experience significant abdominal pain or persistent vaginal bleeding.* [...] *After pains typically reduce in the hours following childbirth and do not develop after discharge. Pain after a vaginal birth that does not settle with simple analgesia should prompt a face to face review and a clinical examination including both abdominal and vaginal examination if indicated*" [4] If there is any concern or repeated presentations to the GP or emergency care, all women must be referred immediately back to the obstetric maternity unit or Accident and Emergency (A&E). *[Evidence level 4]*

5.3 | What is the Optimum way to Monitor Women with Suspected Sepsis?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Monitoring of a woman with suspected sepsis should be performed using an early warning system modified for obstetrics, managed through a multidisciplinary approach with early escalation and senior input.	**4**	**GPP**	This reflects best practice and NICE guidelines on improving the recognition and response to deterioration in unwell adults [47].

Women who become unwell during pregnancy and birth often deteriorate abruptly following a period of physiological compensation [54]. This narrows the window for early detection of developing illness. Early escalation to a senior clinician is recommended for pregnant women. Observations of all vital signs, including temperature, pulse rate, blood pressure, oxygen saturations and respiratory rate, should be recorded on an early warning system [55]. This should be modified for obstetrics to account for the physiological changes of pregnancy. There should be clear instructions for escalation using a structured Situation-Background-Assessment-Recommendation (SBAR) communication tool [54]. *[Evidence level 4]*

5.4 | What are the Common Investigations when Sepsis is Suspected?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Blood cultures are a key investigation and two sets should be obtained prior to antibiotic administration; however, antibiotic treatment should be started without waiting for microbiology results. Consider HSV polymerase chain reaction (PCR) when indicated.	**4**	**D**	The key investigations for suspected sepsis in women during and after pregnancy are described in NG51 [47].
Serum lactate should be measured urgently in women with features making them at high risk of sepsis. Serum lactate of 4 mmol/l or more should prompt immediate escalation of care, including consideration of discussion with the critical care team.	2—	**D**	Recommended by NG51 [47].

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Any relevant imaging studies should be performed promptly to confirm the source of infection. These may include a pelvic ultrasound scan or computer tomography scan if pelvic abscess is suspected, or a chest x-ray for possible chest pathology.	**4**	**D**	Recommended by NG51 [47].
Other microbiological samples taken should be guided by the clinical suspicion of focus of infection as appropriate.	**4**	**GPP**	This would be regarded as best practice.
Routine blood tests should include full blood count, coagulation screen, urea, electrolytes, creatinine, liver function tests (LFT), C-reactive protein (CRP), venous blood gas (or other near patient testing) for glucose and lactate.	**4**	**GPP**	Recommended by NG51 [47].
Appropriate virological testing, including SARS-Cov-2 testing should be undertaken if indicated.	**4**	**GPP**	Follow recommendations of current COVID-19 guidance [2].
Any woman who is unwell with symptoms of tonsillitis/pharyngitis should have a throat swab sent for bacterial culture.	**4**	**GPP**	This would be regarded as best practice to identify GAS infection.
If the MRSA status of the woman is unknown, a premoistened nose swab should be sent for rapid MRSA screening where such testing is available.	**4**	**GPP**	Identification of MRSA is important to guide therapy and infection control measures.

Serum lactate should be measured urgently in women with features indicating a high risk of sepsis to guide care; however, it is recognised that lactate may also be elevated by the physiological process of labour and due to other complications common in pregnancy, such as bleeding. A lactate of 2 mmol/l or more should initiate immediate senior review, intravenous fluid administration and repeat lactate measurement thereafter to gauge response to treatment. Serum lactate of 4 mmol/l or more is indicative of tissue hypoperfusion or cellular metabolic dysfunction. This should prompt immediate escalation of care, including consideration of discussion with critical care regarding ongoing care and intravenous fluid bolus administration [56]. *[Evidence level 3]*

Routine blood tests should include a venous blood gas analysis for lactate and glucose and a full blood count, urea, electrolytes, creatinine, clotting screen, LFT and CRP [56]. The CRP serum level rises with bacterial sepsis, thrombus and post-surgery, and rarely with viral infections (such as SARS-COV-2, influenza and adenovirus pneumonia). While procalcitonin (PCT) levels can help differentiate bacterial from viral infection in non-pregnant women, [57] hormonal resistance to lipopolysaccharide (LPS) activation by the main PCT producers, [58] and a wide range of PCT levels in the setting of PPROM, with a doubling of the normal labour mean values [59] must be considered when results are interpreted.

TABLE 6 | Surviving Sepsis Campaign Hour-1 Bundle of Care Elements [74].

1	Measure lactate level*
2	Obtain blood cultures before administering antibiotics (but do not delay giving antibiotics)
3	Administer broad-spectrum antibiotics
4	Begin rapid administration of 30ml/kg crystalloid for hypotension or lactate level ≥ 4 mmol/L
5	Apply vasopressors if hypotensive during or after fluid resuscitation to maintain mean arterial pressure (MAP) ≥ 65 mm Hg

*Remeasure lactate (within 1 hour) if initial lactate is elevated (> 2 mmol/l).

If LFTs show an anicteric pattern (i.e. markedly raised ALT with normal bilirubin) consider a diagnosis of herpetic hepatitis and treat appropriately, while waiting for results to exclude other causes of hepatitis.

In women at high risk of sepsis these investigations and the initiation of care should commence immediately. Thrombocytosis (high platelet count) with a rising CRP and a swinging pyrexia often indicates a collection of pus or an infected haematoma. *[Evidence level 4]*

5.4.1 | Bacteriology Samples

A though history can help identify the cause of sepsis (Table 7).

Two sets of blood cultures (each set including an aerobic and anerobic bottle) should be taken sequentially, within in minutes of each other. Increasing the volume of blood sampled maximises the aspiration of circulating bacteria and thus the yield of pathogens. Blood cultures should be obtained prior to antibiotic administration and empirical treatment started without waiting for any microbiology results. Consider if a blood sample is indicated for HSV PCR. Other microbiology sampling should be guided by clinical suspicion of the focus of infection. Where testing is available, a nasal in viral transport media may be sent for rapid MRSA molecular diagnostic screening. The alternative is a premoistened nasal swab cultured overnight on selective media. If a woman has a normal CRP or symptoms are more suggestive of a viral respiratory infection (e.g. SARS-CoV2, influenza) then a viral nasal swab should be taken for PCR. Swabs taken from throat, vagina, caesarean or other wounds should be sent for bacterial culture as appropriate. *[Evidence level 4]*

Symptoms of tonsillitis/pharyngitis should prompt a throat swab for bacterial culture. Diarrhoea warrants routine stool culture (e.g. *Salmonella, Campylobacter*) as well as testing for *Clostridium difficile* toxin, [60] the latter especially if diarrhoea follows antimicrobial therapy. An infection specialist should be consulted because of the wide range of highly contagious infections necessitating high-level infection control precautions to protect staff and other patients. The laboratory should be

TABLE 7 | Points to note in history regarding infection that may suggest cause of sepsis.

History	Classic symptoms/features	Microbiological considerations
Febrile illnesses	Chills, rigors, myalgia	Staphylococcal/streptococcal bacteraemia especially if wounds, rash Gram negative infections - if urinary symptoms or recent urinary catherisation Consider influenza (in flu season beware dual infection with secondary bacterial pneumonia) Consider HSV septicaemia even if no other features of herpes present Enteroviral/SARS-Co-V-2/adenoviral infection If recent foreign travel, consult infection specialist urgently (malaria, haemorrhagic fever viruses [75–78] and other high risk viral infections etc.)
Contact with GAS	Impetigo, tonsillitis, cellulitis Flu-like symptoms, diarrhoea, vomiting Rapid deterioration, systemically very unwell Disproportionate pain anywhere in the body with few outward signs warrants consideration of necrotizing fasciitis Late onset after pains [4] Severe abdominal pain also occurs if uterine myonecrosis or GAS peritonitis	GAS
Recurrent skin infections History of or contact with recurrent boils or abscesses	Abscess or severe mastitis Scars from previous incision and drainage	PVL producing *S.aureus* [29, 32]
Severe respiratory infection, hemoptysis	Haemoptysis Cavitation and massive effusions	Tuberculosis [4] Necrotising pneumonia-PVL producing *S. aureus* [68, 69] or GAS [66, 67]
Dysuria, flank pain, pyrexia suggesting urinary tract infection	Flank pain, dysuria, fevers	Check recent antimicrobial treatment and priors sensitivities in case ESBL or CPE history
Acute Urinary Retention	Dysuria, urinary retention, vulval or sacral pain/parasthesiae	HSV
Intravenous drug misuse	Septic emboli-vasculitic lesions, stigmata of endocarditis	GAS, PVL-producing *S. aureus*, MRSA Endocarditis (may present as pneumonia if tricuspid valve endocarditis) *S. aureus* and GAS infections, Immunosuppression of chronic disease Blood borne viruses (HIV, HBV, HCV)
Gastroenteritis	Diarrhoea and vomiting Traditionally crampy abdominal pains are more associated with *Campylobacter spp*. than *Salmonella spp*. in infectious gastrosenteritis	Gastroenteritis – foodborne pathogens, e.g. *Salmonella spp., Campylobacter spp* Early toxic shock (staphylococcal and streptococcal exotoxins acting as enterotoxins) *C. difficile* [60] (especially if recent antibiotics) Viral e.g. Norovirus
Zoonotic infections	Consumption unpasteurised milk products, undercooked or cured meats Exposure to animals with diarrhoea Contact with birthing animals, washing clothes of animal handlers, feeding lambs or bird contact	*Salmonella spp*, Campylobacter, Listeria Campylobacter, *C. difficile*, salmonella, Cryptosporidium As above plus Q fever and *Chlamydophila* (Can be rapidly fatal in pregnancy)

(Continues)

TABLE 7 | (Continued)

History	Classic symptoms/features	Microbiological considerations
History of infection with multi-resistant organisms	ESBL of CPE producing Gram negatives, Methicillin-Resistant *Staphylococcus Aureus* (MRSA), Vancomycin Resistant Enterococci (VRE)	Infection control precautions (e.g. side room) Limits empirical antimicrobial choice *discuss urgently with infection specialist*
Haemorrhagic rash, purpura	Meningococcal, pneumococcal or GAS sepsis most likely If recent foreign travel (or contacts recently returned from abroad) must consider possibility of viral haemorrhagic fever (Lassa Ebola etc.) [75–78]	Discuss urgently with infection specialist Stringent infection control precautions
Allergies	Obtain careful allergy history (Nausea/vomiting = intolerance not allergy)	Ensure genuine allergy history (severe rash or anaphylaxis) otherwise could unnecessarily preclude beta-lactams with a weak history of 'possible' allergy (e.g. vomiting with co-amoxiclav)
	Mild rash with penicillins	1%–3% chance of cross reaction with cephalosporins, carbapenems
	Anaphylaxis with penicillins	Avoid all cephalosporins and carbapenems Discuss with infection specialist but erythromycin, clindamycin or vancomycin may be appropriate alternatives

Abbreviations: CPE, Carbapenemase-producing Enterobacteriaceae; ESBL, Extended spectrum Beta-Lactamase; GAS, Group A beta haemolytic streptococci; HBV, hepatitis B virus; HCV, hepatitis C Virus; HIV, human immunodeficiency virus; MRSA, methicillin-Resistant *Staphylococcus Aureus*; PVL, Panton Valentine Leukocidin; VRE, Vancomycin Resistant Enterococci.

informed if there is a clinical indication for investigations for unusual pathogens e.g consumption of soft cheese or cured meats (*Listeria monocytogenes)*, a history of foreign travel (parasites, malaria, typhoid, cholera, viral haemorrhagic fever, brucella) or hospitalisation (multi-drug resistant organism screening). Microbiology results should be reviewed when available to allow optimisation of the antibiotic regimen and more targeted therapy [61]. *[Evidence level 3]*

If the woman has been on broad-spectrum antimicrobials before developing signs of sepsis it is likely the pathogen is multi-drug resistant, and an infection specialist should be consulted for advice on further antimicrobial options.

Prompt imaging may identify the source of the infection, allowing early definitive treatment, and should not be deferred on the grounds of pregnancy alone. This could include a chest X-ray and, in women following pregnancy, a pelvic ultrasound scan, computed tomography scan or magnetic resonance imaging (MRI) scan if pelvic abscess is suspected. In women at moderate risk of sepsis it is suggested clinical examination and results review should be carried out within 1 hour [56]. *[Evidence level 4]*

5.4.2 | Samples for Viral Infection Diagnosis

Women suspected of having influenza should be tested immediately using a viral nasal/throat swab for influenza PCR, barrier nursed and treated with antivirals while awaiting PCR results [62]. Women suspected of SARS-CoV-2 should be assesses according to the RCOG guidance *Coronavirus (COVID-19) infection in pregnancy* [2]. *[Evidence level 4]*

During 2009–12, an upsurge in influenza combined with a low vaccination rate, diagnostic delay and lack of treatment accounted for 43% of all infection-related deaths in pregnancy (36 women); [5] in stark contrast to only one death during the three years of the subsequent report when vaccination increased, [63] and two in the 2023 MBRRACE report [4].

Influenza related morbidity and mortality is associated with a body mass index (BMI) of over 30 kg/m^2. Early birth may be indicated during the third trimester of pregnancy. Pulmonary haemorrhage due to primary influenza has been reported [64, 65].

Secondary bacterial infection with pneumococci, beta-haemolytic streptococci and *S. aureus* occur typically after influenza and other viral respiratory infections. GAS exotoxins [66, 67] and *S. aureus* associated PVL [68, 69] produce a secondary necrotising haemorrhagic pneumonia with severe respiratory compromise and a high mortality rate [43]. *[Evidence level 3]*

Initiating extra-corporeal membrane oxygenation (ECMO) should be considered in fulminant cases of primary influenza pneumonia or SARS-CoV-2 [4]. The need for updated guidance on referral for ECMO therapy was highlighted in the recent MBRRACE report [4]. For more information on SARS-CoV-2 see the RCOG guidance *Coronavirus (COVID-19) Infection in Pregnancy* [2].

In suspected HSV cutaneous infection, or vulval/sacral pain/parasthesia with no visible lesion, send a viral swab for PCR either from the lesion, or as a vaginal sample. If disseminated HSV and hepatitis is suspected, send an EDTA (Ethylenediamine tetra acetic acid) blood sample for HSV viral PCR. Discuss management with an infection specialist.

5.5 | What are the Appropriate Triggers for the Involvement of Other Specialities and who Should be Involved?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Senior clinicians (obstetricians and obstetric anaesthetist) and a senior midwife should be directly involved in the decision to escalate care within one hour of any deterioration.	**4**	**GPP**	As per NICE guideline (NG51) [47].
Expert multidisciplinary advice should be sought urgently at a senior level when sepsis is suspected and not responding to initial management.	2—	**GPP**	Failiure to rapidly obtain senior multidisciplinary support was highlighted as an area for improvement by MBRRACE-UK [6].
There should be an urgent referral to the critical care team in severe or rapidly deteriorating cases of sepsis where the facilities/skills to care for a woman are not available on the maternity unit.	**3**	**GPP**	Rapid deterioration despite reuscitation measures suggests likely need for intensive care support.

Early consultation with an infection specialist (medical microbiologist or infectious disease clinican) is recommended to optimise microbiological diagnostic investigations and appropriate usage of animicrobials. The decision to transfer a woman to the adult intensive care unit should be made by senior clinicians (obstetricians/anaesthetists) (Table 8). As soon as the need for an enhanced level of care/critical care is recognised that level of care should be provided, regardless of the setting. *[Evidence level 4]*

6 | Managing Maternal Sepsis

6.1 | How should Maternal Sepsis be Managed?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Administration of intravenous broad-spectrum antibiotics is recommended within one hour in women at high risk of sepsis, with or without septic shock.	2—	**C**	As per NICE guideline (NG51) [47].
Use of a sepsis bundle may improve compliance with urgent management in women at high risk of sepsis.	2—	**D**	As per NICE guideline (NG51) [47].
Early fluid resuscitation of crystalloid should be administered with an immediate 500ml fluid bolus in women with hypotension or elevated lactate above 4mmol/L. This may need repeating. When indicated, urine output should be measured with precision using an hourly urometer.	**4**	**D**	
Choice of empirical antibiotic therapy should be guided by local epidemiology reflecting the incidence of resistant organisms within that geographical area. Information about antibiotic therapies and limitations of antimicrobial spectrum are given in Table 9.	**4**	**D**	As per NICE guideline (NG51) [47].
For life threatening sepsis, where the sensitivity of the organism is unknown, a combination of either piperacillin/tazobactam or meropenem (for Gram negative cover) plus clindamycin (for Gram positive and anaerobic organisms) provides very broad cover, but local guidelines should be consulted and discussed if history of multi-resistant organism. With any history of MRSA in a woman with sepsis, the addition of vancomycin is advisable.	**4**	**GPP**	Local guidance should be used to inform treatment choices, but this regimen has been included as an appropriate choice for use when broad cover in required in circumstances when the organism is unknown.
Empirical antimicrobials should be reviewed with culture results and targeted oral agents used as soon as clinically appropriate.	**4**	**D**	Best practice in antimicrobial stewardship should be followed [61].
If a change in antibiotic regimen is considered because of deterioration despite first-line treatment, consider the addition of IV aciclovir 500mg 8 hourly as part of the second-line regimen.	**4**	**D**	As per Coroner's report [9].
Regular senior clinical review is recommended.	**4**	**D**	As per NICE guideline (NG51) [47].

Women who are pyrexial (temperature of 38°C or higher) in labour should be offered a broad spectrum antibiotic regimen, which should cover GBS, in line with local microbiology sensitivities [70–72].

As part of a sepsis bundle, such as the Surviving Sepsis Campaign Hour-1 bundle (Table 6), or the Sepsis-6 bundle (Appendix 4), administration of intravenous broad-spectrum antibiotics within 1 hour is recommended in women at high risk of sepsis [12, 47]. In a UK population-based case-control analysis of non-influenza sepsis-related maternal deaths from 2009–2012, half

TABLE 8 | Indications for transfer to Intensive Care Unit.

System	Indication
Cardiovascular	• Hypotension (< 90 mmHg systolic) or raised serum lactate (> 4 mmol/l) persisting despite fluid resuscitation, suggesting the need for vasopressor and/or inotrope support
Respiratory	• Pulmonary oedema • Need for mechanical ventilation • Need for airway protection
Renal	• Renal replacement therapy
Neurological	• Decreased conscious level
Miscellaneous	• Multi-organ failure • Uncorrected acidosis • Hypothermia

Note: Adapted from Plaat and Wray (2008) [79].

of those who died had no serum lactate measurement. Sixty-seven percent of those who died received antibiotics the same day of diagnosis (c.f 85% controls). Overall, only 33% of those who died received antimicrobials within 1 hour of diagnosis, and 58% within three hours [73]. *[Evidence level 2–]*

Early fluid resuscitation of crystalloid should be administered, starting with a fluid bolus of 500ml in women with hypotension or elevated lactate of more than 4mmol/L [82]. Further fluid boluses may be required based on the response, but ensure intensive care input if more than two litres volume has been required without improvement in hypotension [47]. When indicated, urine output should be measured with a urinary catheter and urometer, recording urine output hourly. Care must be taken in women who also have pre-eclampsia or eclampsia as they are at higher risk of pulmonary oedema; with individualised care guided by close anaesthetic or critical care involvement [83]. *[Evidence level 4]*

During and after pregnancy it should be noted that current systemic infection is an important risk factor for venous thromboembolism and should prompt reassessment for the correct thromboprophylaxis according to current guidelines [80].

Maternal pyrexia is an important potential marker of infection, but may not always be present in maternal sepsis and is not necessarily related to the severity of illness. Indeed, it is important to recognise that sepsis can present with hypothermia. Pyrexia in labour can be managed with supportive measures such as increased fluid intake, paracetamol, tepid sponging and lowering the environmental temperature. Non-sepsis causes of maternal hyperthermia such as epidural anaesthesia and misoprostol are diagnoses of exclusion. Women with a fever during labour should be screened for sepsis as already described, and the underlying source of infection identified and managed [84]. Women with pyrexia and suspected infection in labour should be offered an antibiotic regimen which covers GBS, [70, 71] and they should be offered continuous fetal monitoring [85]. *[Evidence level 3]*

If genital tract sepsis is suspected, GAS and *E.Coli* are likely pathogens [4]. Prompt treatment with a combination of high-dose broad-spectrum intravenous antibiotics, active against Gram-negative bacteria and capable of preventing exotoxin production from Gram-positive bacteria, may be lifesaving. The empirical choice of antimicrobials should be tailored to local epidemiology and resistance. Local formularies should be consulted, narrowing the agent spectrum to that of the causative organism(s) once identified. Early oral switch and a documented duration should be included in the individual's medical notes [61]. Source control should be a priority, e.g. surgery to drain pus, expedited birth where necessary. Women suspected of having infected retained products of conception should be given antibiotics and surgery to remove the infected products of conception should be performed promptly [4]. *[Evidence level 4]*

Increasing resistance of GBS to clindamycin (31% resistance in 2022) has necessitated recommendations for substituting cephalosporins or vancomycin for beta-lactam allergic women needing prophylaxis in labour [44, 71, 72]. Do not use clindamycin for prophylaxis or treatment of GBS infection unless it is known to be sensitive. *[Evidence level 4]*

6.1.1 | Group A Beta-haemolytic Streptococcus

Only 0.03% to 0.06% of pregnant women have perineal colonisation with GAS, and are usually asymptomatic [86]. Vaginal discharge is often watery (leucocytes are destroyed by GAS leucocidins), and not offensive, so may therefore not be thought to be significant. However, ascending vaginally, GAS can cause endometritis, myonecrosis, peritonitis and streptococcal toxic shock syndrome (STSS) [87]. *[Evidence level 4]*

6.1.2 | Necrotising Fasciitis

Post birth wound infection can lead to serious abdominal or remote necrotising fasciitis (NF) [1, 44, 87–92] and STSS [41, 43]. NF refers to infection causing necrosis of the superficial and/or deep fascia and subcutaneous tissue [42, 45] and has been reported to occur in 1.8 per thousand caesarean births [91]. Rare cases of NF following vaginal birth have been reported [4, 42, 43]. The most rapid and severe forms of NF are usually due to GAS. Haematogenous or direct seeding of tissues followed by spread along fascial planes produces few visible external signs in the early stages. Later, tissue oedema and thrombosis of the arterial supply to the nerves contributes to the cardinal feature of NF, namely very severe pain out of proportion to what can be seen. Typically, increasingly stronger analgesia culminating in opioids is an indication of possible NF and regular pain scores should be performed. In late infection, the necrotising process ascends to the surface causing bruising, blisters and finally, obvious necrosis [42, 45].

Bruising in the context of sepsis should raise suspicions of a deeper necrotising process [4, 42, 45]. Following a fatal case of delayed diagnosis of NF following birth by caesarean section, the authors of the MBRRACE report concluded "*unlikely a wound will become bruised a week after surgery without an underlying cause… …Women often have pictures of their wounds ….or they can describe the course of the change if asked…*

TABLE 9 | Antimicrobial choices and limitations of antimicrobial spectrum (see also Appendix 5).

	Spectrum	Points
Co-amoxiclav	No activity against MRSA or Pseudomonas Active against most streptococci, staphylococci (MSSA) anaerobes and many Gram negatives	Concern about an increase in the risk of necrotising enterocolitis in babies exposed to co-amoxiclav in utero
Metronidazole	Only covers anaerobes	Unnecessary if using clindamycin and piperacillin-tazobactam as each covers anaerobes well Used with e.g. cefotaxime as intrapartum prophylaxis for suspected chorioamnionitis if non-severe pencillin allergy [80]
Clindamycin	Currently in the UK covers most GAS (> 89%) [41]; GBS (67%) [71] so should no longer be used for GBS prophlaxis [70] Covers most staphylococci, including many MRSA, and anaerobes Switches off exotoxin production Not renally excreted or nephrotoxic	Associated with increased risk of *Clostridium difficile* superinfection
Piperacillin–tazobactam	Spectrum same as co-amoxiclav, but also many Gram positive and Gram-negative organisms, including pseudomonas No activity against MRSA Renal sparing (in contrast to aminoglycosides) Poor activity against ESBL producing coliforms	Avoid in beta-lactam allergy Very poor CSF penetration
Cephalosporins e.g. Ceftriaxone	No activity against ESBL producing coliforms, pseudomonas or MRSA Cover beta-haemolytic streptococci including GAS and GBS (but not enterococci)	Should not be used if severe beta- lactam allergy Increased risk of *C. diffiicle*
Carbapenems	Very broad empirical cover, most Gram-negatives (including most ESBL-producers, anaerobes) Covers most Gram positives – except MRSA CPE are resistant	Not for severe beta- lactam allergy [76] With moderate beta-lactam allergy < 1% cross reaction [81] Excellent penetration including CSF
Gentamicin	Mainly Gram negative cover (incuding most pseudomonas) No streptococcal, or anerobic cover	Inactivated in pus/anaerobic conditions Nephrotoxic and ototoxic, so usually limited where possible to a stat dose for sepsis. (For endocarditis a lower dose is given twice daily, and then serum levels must be monitored)
Vancomycin	Covers MRSA. Recommended option in severe penicillin allergy for GBS prophylaxis No cover for Gram negatives Not absorbed orally, so always given intravenously unless treating *C.difficile* infection	Serum levels need to be monitored due to the potential for renal and ototoxicity. Too rapid infusion can cause "*red man syndrome"* due to histamine release

Note: Antimicrobials in the table are considered safe in breast-feeding. Note quinolones, tetracyclines and linezolid are not included because they are not considered safe in breastfeeding and there are few indications for using these agents in pregnancy/puerperium. (See Appendix 5 for antibiotic spectra.)
Abbreviations: CPE, carbapenemase producing enterobacterales; CSF, cerebral spinal fluid; ESBL, Extended spectrum Beta-Lactamase; GAS, Group A beta haemolytic streptococci; MRSA, Methicillin-resistant Staphylococcus aureus.

Healthcare professionals should also document the appearances of a wound when assessing it to allow other staff to compare any reported changes." [4]

Women with NF need urgent involvement of a plastic surgeon, an intensivist and an infection specialist. Barrier nursing including masks should be instituted because of the risk of spread of GAS to other patients and healthcare workers [93]. For suspected NF, a combination of intravenous piperacillin-tazobactam or meropenem plus clindamycin covers most bacteria, including GAS, the clindamycin aimed at switching off exotoxin production. Since clindamycin is not renally excreted, there is no need to reduce the dosage in renal failure. If MRSA is likely, vancomycin should be added. *[Evidence level 4]*

Streptococcal TSS presents similarly to staphylococcal TSS except that less than 50% of streptococcal TSS patients have the classical 'sunburn rash' found in 100% of patients with TSS.

6.1.3 | Antimicrobial Management of Sepsis

Information on antimicrobials and spectrum of activity which may aid in guiding choice is given in Table 9. Empirical local hospital guidelines should be consulted as they will reflect local epidemiology, as the incidence of resistant organisms varies with geographical areas. The antimicrobials to include in the hospital formulary and maternity unit guidelines for sepsis in the puerperium should be agreed by clinicians and an infection specialist. *[Evidence level 4]*

For empirical therapy of life-threatening sepsis, a combination of either piperacillin/tazobactam or meropenem (for Gram negative cover) plus clindamycin (for Gram positive and anaerobic organisms) provides very broad cover, but lacks guaranteed MRSA cover. Therefore, if there is any suspicion of MRSA, addition of vancomycin is advisable. Local guidelines should always be consulted. If there is a history of severe beta-lactam allergy, an infection specialist should be consulted. An unwell woman with a history of multi-drug resistant organism carriage or infection (e.g. ESBL/CPE/Vancomycin Resistant Enterococci (VRE), or suspected PVL or iGAS warrants discussion with an infection specialist. Appropriate national guidelines are available on the UK Health Security Agency (UKHSA) website. *[Evidence level 4]*

6.1.4 | Intravenous Immunoglobulins

Recommendation	Evidence quality	Strength	Rationale for the recommendation
IVIG should be considered as part of treatment for Gram positive necrotising infections and toxic shock when other measures are failing. Use should be limited to the sickest women, and administered in a critical care setting, with a blood warming device. The main contraindication to IVIG use is congenital immunoglobulin A deficiency in the mother.	**3**	**D**	Intravenous immunoglobulin (IVIG) has a role in neutralising circulating exotoxins and superantigens in severe unresponsive Gram-positive necrotising infections and toxic shock.

Intravenous immunoglobulin G (IVIG) is not effective or indicated for Gram negative infections or sepsis in general. However, in severe Gram-positive necrotising infections and toxic shock, IVIG has been shown to neutralise circulating exotoxins and superantigens [81, 94, 95]. The combination of IVIG and clindamycin has been reported as synergistic and beneficial [95–97] and is recommended in the Australian and New Zealand guidelines for suspected GAS sepsis in pregnancy [95]. IVIG has been recommended for consideration when other measures are failing [98]. The main contraindication to IVIG use is congenital immunoglobulin A deficiency [98]. *[Evidence level 3]*

Small case series involving Gram-positive exotoxin-related sepsis have reported dramatic improvement with IVIG [95, 96, 99], but data from large trials are lacking. Furthermore, since dosages and timings of administration of IVIG during the septic event differ widely between centres, meaningful interpretation of the published data is difficult. *[Evidence level 3]*

IVIG administration should be reserved for critically ill women with Gram-positive infections and administered in a critical care setting with a blood warming device. Local hospital protocols for replacement therapy in haematology patients may be used. Varying doses of IVIG of up to 2g/kg have been reported in exotoxin-related sepsis in pregnancy with no adverse effects [93, 95, 96, 99].

6.2 | How should the Fetus be Monitored and Timing and Mode of Birth be Decided?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
In a critically ill pregnant woman, birth of the baby can be expedited if it would be beneficial to the woman or the baby or to both. A decision on the timing and mode of birth should be made by a senior obstetrician following discussion with the woman and/or her family if her condition permits.	**4**	**GPP**	Decisions around birth must be individualised and should be led by a senior obstetrician in consultation with the woman.
If preterm birth is anticipated, magnesium sulfate should be considered if indicated and consideration should be given to the use of antenatal corticosteroids for fetal lung maturity in women with sepsis.	**4**	**GPP**	This follows the recommendation in NICE guideline NG25 [100].
During the intrapartum period, continuous electronic fetal monitoring is recommended. Caution is required if considering fetal blood sampling.	**4**	**GPP**	These recommendations are aligned with NG121 [101] and NG229 [85].
An individual risk assessment should be made by a senior anaesthetist with regards to type of anaesthesia, as well as the need for invasive monitoring	**4**	**GPP**	This recommendation is derived from NG121 [101].

The effects of maternal sepsis on fetal wellbeing include the direct effect of infection in the fetus, the effect of maternal illness/shock and the effect of maternal treatment. The risk of neonatal encephalopathy and cerebral palsy is increased in the presence of intrauterine infection [100]. *[Evidence level 2+]*

If preterm birth is anticipated, the use of antenatal corticosteroids for fetal lung maturity in the woman with sepsis can be considered [100–102]. The use of magnesium sulfate is not contraindicated in sepsis, but additional monitoring is advised as hypotension may be exacerbated. It should be used for fetal

neuroprotection if preterm birth is planned within 24 hours, or the woman is in preterm labour. It should be offered to women between 24^{+0} and 29^{+6} weeks of pregnancy and considered up to 33^{+6} weeks of pregnancy [101]. *[Evidence level 1+]*

During the intrapartum period, continuous electronic fetal monitoring is recommended in the presence of maternal pyrexia (defined as a temperature above 38.0°C once, or 37.5°C on two occasions 1 hour apart) [84, 100]. This should also apply to sepsis without pyrexia. Objective evidence of intrauterine infection is associated with abnormal fetal heart monitoring. However, electronic fetal monitoring is not a sensitive predictor of early onset neonatal sepsis [103, 104]. Also consider that CTG changes may serve as an early warning sign for derangements in maternal physiology and organ dysfunction [105]. Caution is required if considering fetal blood sampling, as in women with sepsis the results can be falsely reassuring [100]. *[Evidence level 4]*

Attempting birth in the setting of maternal instability increases maternal and fetal mortality rates, unless the source of infection is intrauterine [106]. The decision on mode of birth should be individualised by the consultant obstetrician, in consultation with the woman, with consideration to severity of maternal illness, the woman's preference, duration of labour, gestational age, fetal wellbeing and viability and response to treatment [100]. *[Evidence level 4]*

6.3 | What are the Neonatal Issues that must be Considered?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Babies of women treated for sepsis during labour, or in the 24 hour period before or after birth, require assessment for risk factors and clinical indicators of neonatal infection.	**4**	**D**	This recommendation is derived from NICE NG195 on neonatal infection [72].
If either the woman or the baby is infected with iGAS disease in the postpartum period, both should be treated with antibiotics.	**4**	**GPP**	This follows advice on management of GAS contacts [17].

It is recommended that babies of women who receive parenteral antibiotic treatment for confirmed or suspected invasive bacterial infection at any time during labour, or in the 24-hour periods before and after the birth, have a careful assessment of risk factors and clinical indicators of possible early-onset neonatal infection to guide investigations and management including antibiotic treatment [72]. *[Evidence level 4]*

Intrapartum antibiotic prophylaxis against GBS should be offered to women with a maternal pyrexia or signs of sepsis during labour [70]. Babies in whom there are any risk factors or clinical indicators of possible early-onset neonatal infection should be cared for as per NICE Guideline [NG195] *Neonatal infection: antibiotics for prevention and treatment* [72].

Specific investigations, management of neonatal infections and advice to parents should be conducted according to NICE Guideline [NG195] [72].

GAS and PVL-producing *S. aureus* infections have been transmitted to babies during birth and breastfeeding, causing severe infection. GAS poses the highest risk of sepsis in the baby, with numerous cases where both the woman and baby have been affected [14, 18]. Therefore, antimicrobial prophylaxis should be routinely given to babies of women with GAS infection [17, 18]. *[Evidence level 4]*

6.4 | What Postnatal Care and/or Infection Control Issues should be Considered?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
All pregnant women and women who have recently given birth should be informed of the signs and symptoms of genital tract infection.	**4**	**GPP**	Good clinical practice.
Any GAS identified during pregnancy should be treated aggressively and full infection control precautions adopted, including barrier nursing as per local guidelines.	**4**	**GPP**	This is guidance from UKHSA [17].
Close household contacts of women with GAS infection should be warned to seek medical attention should symptoms develop, and may warrant antibiotc prophylaxis.	2—	**A**	This is guidance from UKHSA [17].
Healthcare workers who have been exposed to respiratory secretions of women with GAS infection should be considered for antibiotic prophylaxis.	**3**	**GPP**	This is guidance for control of GAS in healthcare and maternity settings [18].

GAS and MRSA are easily transmitted by the hands of healthcare workers and by close contact in households. Local infection control guidelines should be followed for hospital–specific isolation and contact precautions. iGAS infections are notifiable and the infection control team and the UKHSA should be informed [17, 18, 63]. CPE and VRE carriers should be isolated in accordance with local protocols. *[Evidence level 4]*

Women suspected of, or diagnosed with, GAS sepsis should be barrier nursed with protective clothing, including masks, in a single room with en-suite facilities to minimise the risk of spread to other women and staff. Local advice from infection control should be sought [18]. *[Evidence level 4]*

All pregnant women and those who recently gave birth need to be informed of the signs and symptoms of genital tract infection and how to prevent its transmission. Advice to all women should include verbal and written information about GAS prevention, signs and symptoms and the need to seek advice early if concerned, as well as the importance of good personal hygiene being essential. This includes avoiding contamination of the perineum by washing hands before and after using the lavatory or changing sanitary towels. Such emphasis on hygiene is especially necessary when a woman or her family or close contacts have symptoms of GAS infection such as sore throat, impetigo or scarlet fever [17, 18]. *[Evidence level 4]*

Any GAS identified during pregnancy should be treated aggressively. Several cases of women with known GAS infection which was not treated have resulted in maternal death.

7 | Improving Outcomes from Maternal Sepsis

7.1 | Can Sepsis be Prevented or Detected Earlier?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
All pregnant women and women who have recently given birth should be informed of the signs and symptoms of sepsis.	**4**	**GPP**	Good clinical practice.
Healthcare professionals should have a low threshold for suspecting sepsis.	**4**	**GPP**	Good clinical practice.

Any signs of infection or antibiotics administered during a woman's hospital stay should be reported directly to her community carers (GP, midwives and health visitors) on discharge, so that appropriate surveillance can be arranged. *[Evidence level 4]*

7.2 | What Education and Training should be Provided to Health care Providers to Improve Maternal Sepsis Care?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Regular multidisciplinary teaching should be provided to all health professionals involved in caring for women with sepsis.	**4**	**GPP**	This is an important element of continuous professional development and improvement of quality of care.

All clinical staff must undertake regular training for the identification and initial and ongoing management of sepsis. Interprofessional training is preferred [4]. Examples include in-situ and high-fidelity simulation for multidisciplinary team teaching to have a high index of suspicion, early recognition and training to gain leadership and follower skills in a safe environment [48, 55]. *[Evidence level 4]*

8 | Recommendations for Future Research

- Developing and validating pregnancy specific diagnostic criteria and practical screening tools for maternal sepsis.
- Further research is required to quantify the importance of risk factors in predicting the occurrence of sepsis.
- Biomarkers to predict and risk stratify sepsis and related adverse outcomes require further investigation.
- Biomarkers to monitor response to treatment and enable early cessation of antibiotics.
- Studies to understand how best to implement improved quality of care in maternal sepsis in clinical practice.

9 | Auditable Topics

- Proportion of women with suspected sepsis who receive appropriate antibiotic treatment within 1 hour of diagnosis. (100%)
- Proportion of women with suspected sepsis who have blood cultures obtained prior to initiation of antibiotic treatment. (100%)
- Proportion of women with suspected sepsis who have a venous lactate sample obtained within 1 hour of diagnosis. (100%)
- Whether a history of previous multi-drug resistant organisms was checked and influenced the choice of empirical antimicrobials on presentation of maternal sepsis. (100%)
- Proportion of women with GAS identified who are appropriately treated and in whom appropriate contact tracing of household contacts and exposed healthcare workers was carried out. (100%)
- Proportion of women with sepsis occurring in the 24 hours before or after birth, in whom appropriate neonatal treatment was initiated. (100%)

10 | Useful Links and Support Groups

The UK Sepsis Trust: support and eduction for the public, patients and their families affected by sepsis and for health care professionals https://sepsistrust.org

Group B Strep Support: offer information and support to families affected by Group B Strep (and their health professionals), during pregnancy and after birth www.gbss.org.uk

The Lee Spark NF Foundation: support and education for those patients and their families with NF or severe streptococcal infections https://nfsuk.org.uk/

The World Health Organisation "STOP SEPSIS" campaign. Resources for health care providers and links to WHO materials on the prevention and management of maternal sepsis. https://srhr.org/sepsis/

Conflicts of Interest

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

The guideline will be considered for update 3 years after publication, with an intermediate assessment of the need to update 2 years after publication.

Appendix 1

Explanation of Grades and Evidence Levels

Classification of evidence levels	
1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1—	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2—	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

Grades of Recommendation	
A	At least one meta-analysis, systematic reviews or RCT rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Good Practice Points	
GPP	Recommended best practice based on the clinical experience of the guideline development group.*

* on the occasion when the guideline development group find there is an important practical point that they wish to emphasise but for which there is not, nor is there likely to be any research evidence. This will typically be where some aspect of treatment is regarded as such sound clinical practice that nobody is likely to question it. These are marked in the guideline, and are indicated by ✓. It must be emphasised that these are NOT an alternative to evidence-based recommendations, and should only be used where there is no alternative means of highlighting the issue.

Appendix 2

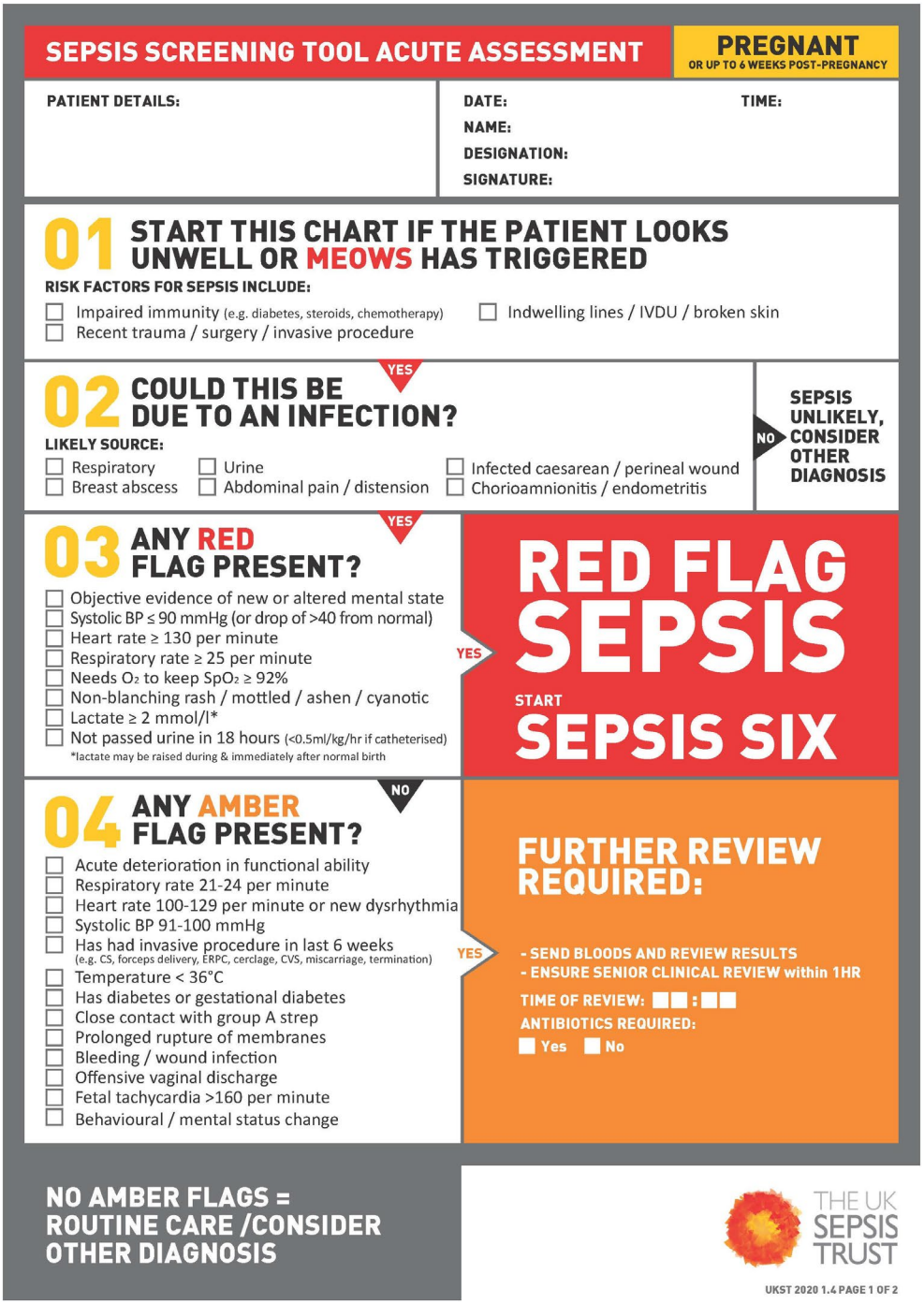
The Sequential Organ Failure Assessment (SOFA) Score [6]

	1	2	3	4
Respiration PaO_2/FiO_2 (mmHg) SaO_2/FiO_2	<400 221–301	<300 142–220	<220 67–141	<100 <67
Coagulation Platelets x 10^3/ mm^3	<150	<100	<50	<20
Liver Bilirubin (mg/ dl)	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular Hypotension[a]	MAP <70mmHg	Dopamine ≤5 or dobutamine (any)	Dopamine >5 or norepinephrine ≤0.1	Dopamine >15 or norepinephrine >0.1
Neurological Glasgow Coma Scale	13–14	10–12	6–9	<6
Renal Creatinine, mg/ dL (mircomol/l) Urine output, ml/24 hour	1.2–1.9(106–170)—	2.0–3.4(171–299)—	3.5–4.9 (300–440) <500	>5.0 (>440) <200

MAP, mean arterial pressure; PaO_2, arterial partial pressure of oxygen; FiO_2, fractional inspired oxygen; SaO_2, peripheral arterial oxygen saturation. [a]Vasoactive medication administered for at least 1 hour (dopamine and norepinephrine μmg/kg/min).
According to the Sepsis-3 criteria, a total score of 2 points or more is associated with life-threatening organ dysfunction and sepsis.
There have been efforts to modify the SOFA score to account for physiological changes during pregnancy, but these have not been well validated [62].

Appendix 3

Example of Maternal Sepsis Risk Stratification Tool



CS, Caesarean section; CVS, Chorionic villus sample; ERPC, Evacuation of retained products of conception; IVDU, Intravenous drug user. Current versions of this tool and additional tools designed for other situations such as community use can be obtained from https://sepsistrust.org

Appendix 4

Example of Maternal Sepsis Bundle Action Tool

SEPSIS SCREENING TOOL - THE SEPSIS SIX

PREGNANT
OR UP TO 6 WEEKS POST-PREGNANCY

PATIENT DETAILS:

DATE: TIME:
NAME:
DESIGNATION:
SIGNATURE:

COMPLETE ALL ACTIONS WITHIN ONE HOUR

01 ENSURE SENIOR CLINICIAN ATTENDS
NOT ALL PATIENTS WITH RED FLAGS WILL NEED THE 'SEPSIS 6' URGENTLY. A SENIOR DECISION MAKER MAY SEEK ALTERNATIVE DIAGNOSES/ DE-ESCALATE CARE. RECORD DECISIONS BELOW
NAME: GRADE:
TIME □□:□□

02 OXYGEN IF REQUIRED
START IF O_2 SATURATIONS LESS THAN 92% - AIM FOR O_2 SATURATIONS OF 94-98%
IF AT RISK OF HYPERCARBIA AIM FOR SATURATIONS OF 88-92%
TIME □□:□□

03 OBTAIN IV ACCESS, TAKE BLOODS
BLOOD CULTURES, BLOOD GLUCOSE, LACTATE, FBC, U&Es, CRP AND CLOTTING
LUMBAR PUNCTURE IF INDICATED
TIME □□:□□

04 GIVE IV ANTIBIOTICS
MAXIMUM DOSE BROAD SPECTRUM THERAPY
CONSIDER: LOCAL POLICY / ALLERGY STATUS / ANTIVIRALS
TIME □□:□□

05 GIVE IV FLUIDS
GIVE FLUID BOLUS OF 20 ml/kg if age <16, 500ml if 16+
NICE RECOMMENDS USING LACTATE TO GUIDE FURTHER FLUID THERAPY
TIME □□:□□

06 MONITOR
USE MEOWS. MEASURE URINARY OUTPUT: THIS MAY REQUIRE A URINARY CATHETER REPEAT LACTATE AT LEAST ONCE PER HOUR IF INITIAL LACTATE ELEVATED OR IF CLINICAL CONDITION CHANGES
TIME □□:□□

RED FLAGS AFTER ONE HOUR – ESCALATE TO CONSULTANT NOW

RECORD ADDITIONAL NOTES HERE:
e.g. allergy status, arrival of specialist teams, de-escalation of care, delayed antimicrobial decision making, variance

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Appendix 5