# NICE guideline review: neonatal infection: antibiotics for prevention and treatment (NG195)

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## BACKGROUND

Neonatal infection has been recognised as the third most common cause of neonatal death globally.[1] In the UK, a retrospective analysis that spanned over 30 neonatal units from 2005 to 2014 found the incidence of neonatal infection was 6.1 per 1000 live births and 48.8 per 1000 neonatal admissions.[2] The incidence of early-onset neonatal sepsis (EONS) in the UK was 0.7 per 1000 live births.[2]

The National Institute for Health and Care Excellence (NICE) published the first guideline (CG149) intended for management of early-onset sepsis in 2012; this has been updated (NG195) in 2021.[3] The guideline refers to the use of Kaiser Permanente Sepsis Risk Calculator (KPSRC), which applies a multivariable modelling approach to predict individualised risk of EONS.[4] The KPSRC has been used widely across the world; published reports indicate a significant reduction in antibiotic use without missing true cases of EONS.[4–6]

## INFORMATION ABOUT THE CURRENT GUIDELINE

The current guideline (NG195) provides new recommendations for intrapartum antibiotics and details the risk factors for infection. It refers to the assessment of risk using the KPSRC, lists the clinical indicators of possible infection and recommends management of late-onset neonatal sepsis (LONS).

This guideline should be used in conjunction with existing NICE guidelines on meningitis (bacterial) and meningococcal septicaemia in under 16s (CG102), urinary tract infection (CG54), sepsis (NG51), fever in under 5s (NG143) and specialist neonatal respiratory care for babies born preterm (NG124) (see box 1).

This review encompasses recommendations for both EONS and LONS.

## KEY ISSUES THAT THE GUIDELINE ADDRESSES

- Recognition and management of pregnant women whose unborn baby is at risk of infection.
- Prevention of bacterial infection in healthy neonates up to and including 28 days' corrected gestational age.
- Treatment of neonates with suspected or confirmed bacterial infection.

### Definitions

- EONS refers to an infection occurring before 72 hours after birth.
- LONS refers to an infection occurring after 72 hours after birth.
- Red flag indicators refer to the highest risk factors that need immediate treatment.
- Non-red flag clinical indicators refer to risk factors that can have causes other than neonatal infection and therefore do not always signal the need for immediate treatment with antibiotics.

### Assessment

#### Prevention of EONS before birth

Women in labour should be offered intrapartum antibiotics when any of the following factors are present:

- Preterm labour.
- Group B streptococcal (GBS) colonisation, bacteriuria or infection in the current pregnancy.
- GBS colonisation, bacteriuria or invasive GBS infection herself in a past pregnancy, but does not have a negative high vaginal swab (HVS) result for GBS in the current pregnancy.
- Previous baby with an invasive GBS infection.
- Clinical diagnosis of chorioamnionitis.

Immediate delivery (induction or caesarean section) should be offered to women who are at 34–37 weeks'

**Box 1 Resources**

- Neonatal infection: antibiotics for prevention and treatment (National Institute for Health and Care Excellence guideline 2021): https://www.nice.org.uk/guidance/ng195
- Fever in under 5s: assessment and initial management (National Institute for Health and Care Excellence guideline 2019): https://www.nice.org.uk/guidance/ng143
- Sepsis: recognition, diagnosis and early management (National Institute for Health and Care Excellence guideline 2016): https://www.nice.org.uk/guidance/ng51
- Neonatal infection (early onset): antibiotics for prevention and treatment (National Institute for Health and Care Excellence guideline 2012): https://www.nice.org.uk/guidance/cg149
- Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management (National Institute for Health and Care Excellence guideline 2010): https://www.nice.org.uk/guidance/cg102
- Urinary tract infection in under 16s: diagnosis and management (National Institute for Health and Care Excellence guideline 2007): https://www.nice.org.uk/guidance/cg54
- Specialist neonatal respiratory care for babies born preterm (National Institute for Health and Care Excellence guideline 2019): https://www.nice.org.uk/guidance/NG124

gestational age with prolonged rupture of membranes (PROM) and with GBS colonisation.

### Assessment of babies after birth

- Babies should have physical examination including recording of vital signs as part of risk assessment when there are risk factors for (see table 1) or clinical indicators of (see table 2) infection.
- Babies with any red flag indicators, or with two or more 'non-red-flag' risk factors or clinical indicators, should start antibiotic treatment.
- The NICE guideline advises the KPSRC may be used as an alternative method for risk assessment for EONS in babies born after 34 weeks' gestation, but only in the context of a prospective clinical audit recording:
  1. Total number of babies assessed.
  2. Number correctly identified as having culture-positive infection and the number of babies incorrectly identified by the KPSRC who do not develop a culture-confirmed neonatal infection.
  3. Number of babies missed by the calculator who develop a culture-confirmed neonatal infection.

### Investigations

- Investigations for suspected EONS/LONS are based on risk factors and clinical indicators and are outlined in table 3.
- Neonates readmitted from the community with LONS should be investigated as per the NICE sepsis guideline (NG51).[7]

### Management

- In all babies, administer antibiotics within 1 hour of the decision to treat (EONS and LONS).
- For babies under the care of neonatal units:
  - Manage suspected neonatal sepsis as outlined in table 4.
  - Babies with purulent eye discharge should start treatment for possible gonococcal infection (EONS).
  - In suspected umbilical infection, such as purulent discharge or redness/swelling, perform a blood culture, take umbilical swab and start intravenous flucloxacillin with gentamicin (EONS).
  - Add anaerobic cover (eg, metronidazole) in addition to flucloxacillin and gentamicin if necrotising enterocolitis is suspected (LONS).
- Antibiotic regimen for neonates readmitted from the community should include cefotaxime and amoxicillin (LONS).[7]

## WHAT DO I NEED TO KNOW

### What should I stop doing?

For EONS

- C reactive protein (CRP) rise of ≥10 mg/L should not be considered as a marker for performing a lumbar puncture.
- Suspected or confirmed maternal infection should not be considered as a 'red flag'; it is an 'other' risk factor.
- Isolated respiratory distress for >4 hours should not be considered a 'red flag' indicator.

**Table 1** Risk factors for neonatal sepsis

| Early-onset neonatal infection | Late-onset neonatal infection |
|---|---|
| *Red flag risk factor*<br>► Suspected /confirmed infection in another baby in the case of a multiple pregnancy.<br>*Other risk factors*<br>► Invasive GBS infection in a previous baby or maternal GBS colonisation, bacteriuria or infection in the current pregnancy.<br>► Preterm birth following spontaneous labour before 37 weeks' gestation.<br>► Confirmed rupture of membranes for >18 hours before a preterm birth.<br>► Confirmed prelabour rupture of membranes at term for more than 24 hours before the onset of labour.<br>► Intrapartum fever >38°C if there is suspected or confirmed bacterial infection.<br>► Clinical diagnosis of chorioamnionitis. | ► Prematurity.<br>► Mechanical ventilation.<br>► History of surgery.<br>► Presence of a central catheter.<br>► When one baby from a multiple birth has infection. |

GBS, group B streptococcus.

**Table 2** Clinical indicators of neonatal infection

| Assessment category | Early-onset neonatal infection | Late-onset neonatal infection |
|---|---|---|
| Behaviour | ► Altered behaviour or responsiveness. | ► Parent or caregiver concern for change in behaviour.<br>► Appears ill to a healthcare professional.<br>► Does not wake, or if roused does not stay awake.<br>► Weak, high-pitched or continuous cry. |
| Neurology | ► Seizures*.<br>► Altered muscle tone (eg, floppiness).<br>► Signs of neonatal encephalopathy. | ► Seizures.<br>► Bulging fontanelle. |
| Respiratory | ► Apnoea*.<br>► Need for mechanical ventilation*<br>► Signs of respiratory distress (including grunting, recession, tachypnoea).<br>► Hypoxia (eg, central cyanosis or reduced oxygen saturation level).<br>► Persistent pulmonary hypertension of the newborn. | ► Respiratory rate ≥60 breaths per minute.<br>► Grunting.<br>► Apnoea.<br>► Oxygen saturation <90% in air or increased oxygen requirement over baseline. |
| Circulation and hydration | ► Signs of shock*.<br>► Need for cardiopulmonary resuscitation*.<br>► Abnormal heart rate (bradycardia or tachycardia). | ► Persistent tachycardia (heart rate ≥160 beats per minute).<br>► Persistent bradycardia (heart rate <100 beats per minute). |
| Skin | ► Jaundice within 24 hours of birth. | ► Mottled or ashen appearance.<br>► Cyanosis of skin, lips or tongue.<br>► Non-blanching rash of skin. |
| Feeding | ► Feeding difficulties or feed refusal.<br>► Feed intolerance, including vomiting, excessive gastric aspirates and abdominal distension. | ► Alterations in feeding pattern.<br>► Abdominal distension. |
| Abnormal body temperature (unexplained by environmental factors) | ► Temperature <36°C or >38°C. | ► Temperature <36°C or ≥38°C. |
| Other(s) | ► Unexplained excessive bleeding, thrombocytopaenia or abnormal coagulation.<br>► Altered glucose homeostasis (hypoglycaemia or hyperglycaemia).<br>► Metabolic acidosis (base deficit of ≥10 mmol/L). | – |

*Red flag clinical indicators.

**What should I start doing for all neonates?**

For EONS and LONS

- Use clinical judgement, poor response to antibiotics or positive blood culture (excluding coagulase-negative staphylococcus) as an indicator to consider a lumbar puncture.
- Consider the possibility of LONS in babies with clinical indicators of infection presenting ≥72 hours after birth.
- If continuing antibiotics >36 hours (EONS) or 48 hours (LONS) with negative blood culture, perform daily review and consider stopping antibiotics when the baby appears clinically well and the CRP trend is reassuring.
- In babies with positive blood cultures (other than coagulase-negative staphylococcus or a suspected common commensal), antibiotics should be administered for at least 7 days.

**Table 3** Investigations for babies under the care of neonatal unit

| | Early-onset neonatal sepsis | Late-onset neonatal sepsis |
|---|---|---|
| Blood culture | Always, before antibiotics. | Always, before antibiotics. |
| C reactive protein | Before starting antibiotics, repeat after 18–24 hours. | Before starting antibiotics, repeat after 18–24 hours. |
| Lumbar puncture if there is strong clinical suspicion of meningitis, OR positive blood culture, OR poor response to antibiotics | Yes. | Yes. |
| Urine culture | Not indicated. | Only for babies presenting from community (not for babies still in neonatal unit). |
| Skin swabs | Not indicated. | Not indicated. |
| Swab of conjunctival discharge | If discharge is purulent (for chlamydia and gonococcus). | – |
| Swab of umbilical discharge | If discharge is purulent or signs of periumbilical cellulitis. | – |

**Table 4** Management of suspected neonatal sepsis in babies under the care of neonatal unit

| Treatment | Early-onset neonatal sepsis | Late-onset neonatal sepsis |
|---|---|---|
| Antibiotic choice*. | ► Benzylpenicillin two times per day and gentamicin every 36 hours. | ► Flucloxacillin and gentamicin. |
| When using gentamicin†. | ► Dose of 5 mg/kg every 36 hours is recommended.<br>► Second dose should be given if the baby appears unwell or culture has identified Gram-negative bacteria.<br>► Trough concentration should be taken before second dose, and dose intervals aimed to achieve concentration <2 mg/L.<br>► If regimen exceeds three doses, aim for trough concentration of <1 mg/L. | |
| Choice of antibiotics when meningitis is suspected but pathogen is unknown*. | ► Amoxicillin and cefotaxime. | ► Amoxicillin and cefotaxime. |
| Stop antibiotics if blood culture is negative and clinical assessment/C reactive protein is reassuring. | ► At 36 hours. | ► At 48 hours. |
| Perform a daily review to consider stopping antibiotics depending on clinical suspicion, the baby's clinical progress and laboratory results. | ► If continuing antibiotics >36 hours. | ► If continuing antibiotics >48 hours. |
| If blood culture is positive, or where strong suspicion of sepsis remains but with negative culture†. | ► Give antibiotics for 7 days (or longer if the baby has not clinically recovered, on microbiology advice or with certain infections). | |
| If the causative pathogen has been identified†. | ► Change antibiotics according to microbiology advice and sensitivities. | |
| Antifungal cover. | – | ► Prophylactic nystatin if birth weight <1.5 kg or were born <30/40. |

*Antibiotic combinations used may be influenced by local microbiological surveillance data.
†Same criteria applicable to both early-onset and late-onset neonatal sepsis.

### What can I continue to do as before?

For EONS

- Take blood cultures before administering antibiotics.
- Administer antibiotics within 1 hour of the decision to treat.
- Monitor CRP trend and repeat levels at 18–24 hours after starting antibiotics.
- Perform investigations and start antibiotics in babies with one red flag or two or more 'non-red flag' risk factors/clinical indicators.
- Suspected/confirmed infection in another baby in a multiple pregnancy should be considered as a 'red flag' indicator.
- Empirically prescribe benzylpenicillin and gentamicin as first-line antibiotics.
- Consider stopping antibiotics at 36 hours if blood cultures are negative, CRP trends are reassuring and the baby appears well.
- Consider confirmed (not suspected) prelabour rupture of membranes of >24 hours in a term infant or >18 hours in a preterm infant as a 'non-red flag' risk factor.

### What should I do differently?

For EONS

- Initiate discussion with the obstetrics team focusing on offering immediate delivery (induction or caesarean section) to women who are 34–37 weeks with PROM and who had GBS colonisation at any time during the pregnancy.
- Liaise with maternity teams to offer antibiotics during labour to women who have had GBS colonisation in a previous pregnancy, unless a recent negative swab result is available.
- Advise women who are GBS-positive that in future pregnancies there is an increased risk of EONS with GBS affecting the new baby. The general practitioner should be informed of this in writing.
- Consider apnoea or the need for cardiopulmonary resuscitation as a 'red flag' indicator to start antibiotics.

## CRITICAL APPRAISAL

The latest version of the NICE guideline (NG195) recommends some changes in clinical practice and introduces the KPSRC as a possible option to determine risk of neonatal infection, although with some specific caveats. There remain considerable challenges for clinicians caring for the newborn.

### Use of KPSRC in the UK setting

The NICE guidance discusses the KPSRC as an alternative to the NICE criteria for risk assessment in EONS; however, it is highlighted that the KPSRC should only be used as part of a prospective audit. NICE has not suggested using the KPSRC as the main method of risk stratification as there are significant differences in healthcare settings between the US and UK clinical practice. These include the following:

- HVS for detecting GBS colonisation, an essential component of the KPSRC, is currently not offered to all pregnant women. However, the KPSRC formula and algorithm take into account 'unknown' GBS status as well.
- Normal newborn care is midwife-led. Significant workforce and training implications may arise if all babies on the KPSRC pathway have regular observations safely and efficiently.

There are UK data indicating that judicious adaptation of the KPSRC, backed by a robust surveillance programme, enhanced in-hospital observation, and staff and parent education, will be safe in the National Health Service set-up.[4] When considering introduction of the KPSRC in their clinical practice, it would be for individual trusts to determine whether the risks relating to diagnosis outweigh the benefits of earlier discharge and better patient flow-through.

### Viral sepsis

Management of babies with viral infections would benefit from being addressed in future revisions of the NICE guidance. A Dutch study over 12 years reported the incidence of viral infections as 1% for all admissions to neonatal units, accounting for 5%–6% of LONS.[8] A recent prospective cohort study from Ireland showed almost 13% of all preterm infants treated for LONS had human parechovirus.[9] Recent advances in molecular diagnostics have made possible rapid diagnosis of viral infections; specific guidance regarding management of viral sepsis would be valuable.

### Ideal inflammatory marker for bacterial infection

A definitive one remains elusive. Many studies have shown promising results with novel markers including procalcitonin, interleukin 6, interleukin 8 and CD64 for EONS.[10 11] CRP remains the 'late specific marker' recommended by the Guideline Development Group (GDG).[3] The GDG was unable to advocate a particular cut-off level above which CRP values should trigger concerns. A diagnostic test with greater sensitivity and specificity could lead to shorter duration of antibiotics, especially when blood cultures are negative.[9] Multicentre, large-scale studies are needed to establish the benefit of these novel markers in clinical practice.[10 11]

### Need for availability of blood culture results at 36 hours

The revised guideline continues to recommend cessation of antibiotics at 36 hours in suspected EONS following a negative blood culture report. In 2017, a national survey of all microbiology laboratories across the UK identified that at 36 hours blood culture results were available out-of-hours in only 26.6% of centres for a positive result, and 47.5% for a negative result.[12] Standardisation of reporting times across the UK would assist successful implementation of the NICE guideline and achieving antimicrobial stewardship.

### EONS and respiratory pathology

Respiratory distress can occur in up to 7% of term newborns, with increase in incidence in premature neonates.[13] Recommendations regarding use of lung ultrasound to exclude conditions including transient tachypnoea and respiratory distress syndrome may be useful in future guidelines.[14 15]

## CLINICAL BOTTOM LINE

- Intrapartum antibiotics should be offered to women in labour when appropriate.
- Women between 34 and 37 weeks of gestation with PROM together with GBS colonisation/bacteriuria/infection should be offered immediate delivery.
- Antibiotics need to be administered within 1 hour of the decision to treat.
- The KPSRC may be used for risk assessment for EONS in babies >34 weeks of gestation as part of a prospective audit.
- Babies should be reviewed daily and need for continuing/stopping antibiotics should be assessed at each review.
- Babies with positive blood culture (other than coagulase-negative staphylococcus or suspected common skin commensal) without meningitis should be treated with antibiotics for 7 days.
- Decision for lumbar puncture should not be based on a specific CRP cut-off value.
- Parents should be involved in the management of babies with suspected/confirmed sepsis.

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