
Surveillance report
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Surveillance decision

We will plan an update of the following sections of the guideline:

- **Risk factors for infection and clinical indicators of possible infection.**
- **Intrapartum antibiotics.**
- **New area: maternal group B streptococcus status to guide the decision on timing of delivery in women with preterm prelabour rupture of membranes.**

An extension to the scope will be needed to cover antibiotic treatment for late-onset neonatal infection.

We will amend the guideline to:

- Remove references to 'NICE clinical guideline 55', which has now been replaced by NICE's guideline on [intrapartum care for healthy women and babies](https://www.nice.org.uk/guidance/cg190) (NICE guideline CG190).
- Cross-refer to NICE's guideline on [preterm labour and birth](https://www.nice.org.uk/guidance/cg190) at relevant points.
- Modify tables 1 and 2, in section 1.2.1 'Recognising risk factors and clinical indicators', to group the red flags at the top of the table and to indicate the red flags more clearly (such as using the word 'Red flag' instead of 'Yes').

**Reason for the decision**

We found 57 studies through surveillance of this guideline.

New evidence that could affect recommendations was identified. Topic experts, including those who helped to develop the guideline, advised us about whether the following sections of the guideline should be updated and any new sections added:

**Risk factors for infection and clinical indicators of possible infection**

- Which maternal and fetal risk factors for early-onset neonatal infection/sepsis should be used to guide management?

NICE's guideline on [neonatal infection (early onset)](https://www.nice.org.uk/guidance/cg190) includes a table of risk factors for early-onset neonatal infection. The table does not currently list maternal obesity as a risk factor. Evidence identified at the 4-year surveillance review suggested that, after adjusting for maternal
comorbidities (diabetes, gestational diabetes, hypertension, and preeclampsia), there was a significantly higher incidence of sepsis among newborns of obese women than women of a healthy weight. Topic experts had some concerns about the evidence, for example it was not clear how much of the reported infection was early onset, almost a third of participants were excluded for having no BMI data, and the study was from the USA therefore may not be fully generalisable to the UK. However the experts stated that although the evidence from the 4-year review in isolation does not warrant a change to recommendations, this issue should be examined further.

Topic experts raised some additional concerns about risk factors. They noted that the wording and interpretation of some current risk factors and red flags in the guideline (particularly those concerning maternal infection, intrapartum fever, and parenteral antibiotics) may have led to increasing, and in some cases unnecessary, use of antibiotics in infants. A related issue was noted to be the increasing awareness of sepsis, which may have led to a rise in maternal intravenous antibiotics – a knock-on effect being rising use of antibiotics in infants. These issues will need to be examined and impact on the guideline considered. It was noted that NICE’s guideline on sepsis (whose scope and recommendations include pregnant women) should be considered during assessment of any impact.

**Decision:** This review question should be updated.

**Intrapartum antibiotics**

- What is the effectiveness of intrapartum antibiotic prophylaxis in the prevention of early-onset neonatal infection (compared to no treatment)?

A difference was identified between the Royal College of Obstetricians and Gynaecologists Green-top Guideline 36 ('The prevention of early-onset neonatal group B streptococcal disease') and NICE’s guideline on neonatal infection.

- The Green-top Guideline 36 says 'Antibiotic prophylaxis for group B streptococcus is unnecessary for women with preterm rupture of membranes'. It further notes 'Antibiotic administration specifically for group B streptococcus colonisation is not necessary prior to labour and should not be given 'just in case'. If these women are known to be colonised with group B streptococcus, intrapartum antibiotic prophylaxis should be offered.'

- The NICE guideline says 'Consider intrapartum antibiotic prophylaxis using intravenous benzylpenicillin to prevent early-onset neonatal infection for women in preterm labour if there is prelabour rupture of membranes of any duration.'
Topic experts agreed there is a discrepancy and that local practice is split. They noted that there is not good evidence in this area and it has been interpreted differently by the Royal College and NICE. Given the current differences between the 2 guidelines, it would be useful to look again at the evidence.

**Decision:** This review question should be updated.

**Maternal group B streptococcus status to guide the decision on timing of delivery in women with preterm prelabour rupture of membranes**

- New review question – What is the clinical and cost effectiveness of immediate delivery versus expectant management in women with preterm prelabour rupture of membranes and vaginal group B streptococcus colonisation?

NICE's guideline on neonatal infection recommends that intrapartum antibiotic prophylaxis should be considered in women with preterm prelabour rupture of membranes, but no mention is made of assessing their group B streptococcus colonisation status, or considering immediate or delayed delivery based on this status. Evidence identified at the 4-year review indicates that in women with prelabour rupture of membranes between 34 and 37 weeks who have group B streptococcus vaginal colonisation, immediate delivery appears to reduce risk of early-onset neonatal sepsis. While in non-colonised women, labour induction could be delayed until 37 weeks. Topic experts stated that this issue warranted further investigation.

**Decision:** This review question should be added.

**Scope extension**

- Extension of scope to cover antibiotic treatment for late-onset neonatal infection.

The following placeholder statement was published as part of quality standard 75 Neonatal infection (December 2014): Quality statement 6 (placeholder) – Antibiotic treatment for late-onset neonatal infection.

The statement notes that there is a need for evidence-based guidance on the appropriate use of antibiotics in late-onset neonatal bacterial infection (infection arising more than 72 hours after birth). Topic experts were unanimous about the need for guidance in this area. This goes beyond the remit of NICE's guideline on neonatal infection which covers early-onset neonatal infection (defined as within 72 hours of birth). An extension of the scope is therefore needed to cover antibiotic treatment for late-onset neonatal infection.
Decision: The scope should be extended.

Other clinical areas

We also found new evidence that was not thought to have an effect on current recommendations. This evidence related to information and support, avoiding routine use of antibiotics in the baby, investigations before starting antibiotics in the baby, duration of antibiotic treatment, and antibiotics for suspected infection.

We did not find any new evidence related to therapeutic drug monitoring for gentamicin, or care setting.

Equalities

No equalities issues were identified during the surveillance process.

Overall decision

After considering all the new evidence and views of topic experts, we decided that a partial update and a modified scope is necessary for this guideline.

See how we made the decision for further information.
Commentary on selected new evidence

With advice from topic experts we selected 3 studies for further commentary.

Investigations before starting antibiotics in the baby and duration of antibiotic treatment – Single C-reactive protein measurement at 18 hours

We selected the prospective cohort study by Lacaze-Masmonteil et al. (2014) for a full commentary because the study was highlighted as important by topic expert feedback, and there is a potential impact on recommendations in NICE’s guideline on neonatal infection (early onset) about when to assess and how to interpret CRP levels.

What the guideline recommends

When starting antibiotic treatment in babies with risk factors for infection or clinical indicators of possible infection, NICE’s guideline on neonatal infection recommends performing a blood culture before administering the first dose, and measuring the CRP concentration at presentation and again 18–24 hours later.

It recommends considering stopping the antibiotics at 36 hours if:

- the blood culture is negative, and
- the initial clinical suspicion of infection was not strong, and
- the baby’s clinical condition is reassuring with no clinical indicators of possible infection, and
- the levels and trends of CRP concentration are reassuring.

Methods

The prospective cohort study by Lacaze-Masmonteil et al. (2014) examined whether a single CRP measurement at 18 hours of age was able to identify neonates in whom antibiotics started for possible early-onset sepsis could safely be stopped. Babies were eligible for the study if they had at least 1 of the following risk factors for early-onset sepsis: (1) less than 37 weeks’ gestation with either spontaneous preterm labour or preterm and prelabour rupture of the membranes; (2) 35 or more weeks’ gestation with positive maternal group B streptococcus screening and inadequate perpartum antibiotic prophylaxis; (3) any gestational age with prolonged rupture of membranes (more than 18 hours) or clinical chorioamnionitis. The study included 647 preterm (less than
35 weeks' gestation) and 555 late preterm (35–36 weeks' gestation) or term newborns. CRP levels were measured between 15–21 hours of age.

Results

Among the 645 neonates with an 18-hour CRP level less than 10 mg/litre, 1 had proven early-onset sepsis, 43 had possible early-onset sepsis and 601 (93%) were not infected. Among the 557 neonates with an 18-hour CRP level greater than 10 mg/litre, 15 had proven early-onset sepsis, 64 had possible early-onset sepsis, and 478 (86%) were not infected. All infants (n=189) older than 34 weeks' gestation, asymptomatic within 18 hours of age, and with an 18-hour CRP less than 10 mg/litre, were not infected (except 1 asymptomatic infant classified as possible sepsis because antibiotics were continued following bacteraemia in the mother).

Sensitivity and specificity of 18-hour CRP for proven or possible early-onset sepsis were 64% (95% confidence interval [CI] 56 to 73%) and 56% (95% CI 53 to 59%) respectively. The negative predictive value was 93% (95% CI 91 to 95%), and the positive predictive value was 14% (95% CI 11 to 17%).

Strengths and limitations

Strengths

- All healthcare providers were kept unaware of the CRP results during the study period, which may have helped to minimise bias.

Limitations

- It was not reported if the CRP test was interpreted and logged before the culture result was known, which has the potential to introduce bias.

- Blood cultures were taken for use as the reference standard, but the study did not discuss culture results as part of any decision to stop antibiotics. The culture result is a key consideration in NICE's guideline on neonatal infection.

- The inclusion criteria for the study were based on maternal and neonatal risk factors for early-onset sepsis, not all of which align directly with the risk factors noted in the guideline.

- 'Possible sepsis' was defined as the clinician continuing antibiotics for more than 72 hours (despite a negative blood culture) in infants born to mothers who had received intrapartum
antibiotics. No additional clinical or laboratory correlates were obtained, introducing some uncertainty into this categorisation.

- The study was in Canada where pathogens may be different (topic experts suggested a higher percentage of group B streptococcus in the UK).

Impact on guideline

In the study, all neonates (except 1) who were more than 34 weeks' gestation, asymptomatic at 18 hours of age, and had an 18-hour CRP of less than 10 mg/litre were uninfected. The study authors therefore concluded that these criteria could be used to stop antibiotics at 24 hours rather than at 48–72 hours, though they did not go on to validate the criteria. The authors also noted that elevated 18-hour CRP in isolation should not be used as a reason to prolong antibiotics.

NICE's guideline on neonatal infection recommends measuring CRP 18–24 hours after presentation, but it is not until 36 hours after commencing antibiotics that the guideline recommends using levels and trends of CRP, alongside the blood culture result and other factors, to inform a decision to consider stopping antibiotics.

Topic experts noted that although it is important to consider any evidence that could lead to less antibiotic use, the sensitivity and specificity of the 18-hour CRP test was low. It may not therefore be an appropriate measure to use in isolation for diagnostics or to decide antibiotic course length. The experts further noted that many neonatal units have not been able to implement 36 hour reports on blood cultures (and have retained 48 hour reports) and would likely find it difficult to move to a decision rule based on CRP only. The study did not examine interpreting CRP tests in the context of blood culture results. Further research is needed to examine the role of blood cultures, and to validate the 18-hour CRP test alongside other criteria for stopping antibiotics. For these reasons, the study is unlikely to impact on current recommendations.

Investigations before starting antibiotics in the baby and duration of antibiotic treatment – Effects of implementing NICE's guideline on neonatal infection in a single UK neonatal unit

We selected the before-and-after study by Mukherjee et al. (2015) for a full commentary because the study was highlighted as important by topic expert feedback. It is of direct relevance to NICE’s guideline on neonatal infection in reporting potentially negative effects of local implementation of the guideline.
What the guideline recommends

When starting antibiotic treatment in babies with risk factors for infection or clinical indicators of possible infection, NICE’s guideline on neonatal infection recommends performing a blood culture before administering the first dose, and measuring the CRP concentration at presentation and again 18–24 hours later.

It further recommends considering performing a lumbar puncture in a baby who did not have a lumbar puncture at presentation who is receiving antibiotics, if it is thought safe to do so and if the baby:

- has a CRP concentration of 10 mg/litre or greater, or
- has a positive blood culture, or
- does not respond satisfactorily to antibiotic treatment.

It recommends considering stopping the antibiotics at 36 hours if:

- the blood culture is negative, and
- the initial clinical suspicion of infection was not strong, and
- the baby's clinical condition is reassuring with no clinical indicators of possible infection, and
- the levels and trends of CRP concentration are reassuring.

Methods

The before-and-after study by Mukherjee et al. (2015) investigated the effect of implementing NICE’s guideline on neonatal infection on the number of investigations, length of stay and duration of antibiotics in a single UK neonatal unit. The particular focus of the study was the guideline's recommendation to perform a second CRP measurement 18–24 hours after presentation, and the subsequent recommendation to consider a lumbar puncture in a baby who did not have one at presentation guided by (among other criteria) the CRP level.

Infants who had septic screens for early-onset sepsis risk factors were retrospectively evaluated using hospital records and a neonatal database. Two time periods were compared: a 2-month period before the NICE guideline was published (n=76 infants), and another 2-month period after the guideline had been locally implemented (n=66 infants).
Results

After implementing NICE guidance, the number of second CRP tests performed increased from 45% in period 1 to 97% in period 2. In period 2, repeat CRP values were higher in 58% of babies. Lumbar punctures performed increased from 14% in period 1 to 23% in period 2. Hospital stays of 72 hours or less among screened babies decreased from 38% in period 1 to 18% in period 2. However, hospital stays of more than 5 days increased from 21% to 28%. It was stated that antibiotic use increased in period 2, though numerical data were not reported for this outcome. No statistical analysis of the changes in value for any outcomes was performed.

Prolonged rupture of membranes (more than 24 hours) was the most common risk factor in both the groups. There were no positive blood cultures or lumbar punctures.

Strengths and limitations

Strengths

- The study is directly relevant in examining the implementation and subsequent impact of NICE's guideline on neonatal infection.

Limitations

- The study was a retrospective examination of records of 142 infants and no statistical analysis of the data was reported.
- The study was performed in a single neonatal unit, and may not reflect implementation in other settings.
- The local protocol used at the neonatal unit before the NICE guidance was introduced was not reported, therefore interpretation and wider applicability of these findings is unclear.
- Inclusion and exclusion criteria were not explicit, particularly regarding sepsis risk factors. The most common risk factor reported was prolonged rupture of membranes, whereas the risk factor in NICE's guideline on neonatal infection is prelabour rupture of membranes. Topic experts noted that including prolonged rupture of membranes as a risk factor will have included a range of healthy babies in whom tests such as CRP have reduced positive predictive value.
- Topic experts noted that the clinical discretion advocated in the guideline may not have been applied in this study. For example, the authors appeared to have interpreted recommendation 1.7.1.2 as mandating a lumbar puncture if the second CRP was greater than 10 mg/litre.
Whereas the recommendation wording uses the verb 'consider' to indicate weak evidence and when clinicians should employ judgment (see 'Making decisions using NICE guidelines').

- Topic experts also noted that the authors appear to have extended the recommendation to include well, asymptomatic babies. This was not the intent of the guideline which recognises the very low yield of any lumbar punctures in babies who are well and asymptomatic at presentation: Recommendation 1.5.1.3 – 'Perform a lumbar puncture to obtain a cerebrospinal fluid sample before starting antibiotics if it is thought safe to do so and there is a strong clinical suspicion of infection, or there are clinical symptoms or signs suggesting meningitis.'

**Impact on guideline**

The study indicates that implementation of NICE’s guideline on neonatal infection in a particular unit led to increases in investigations, lumbar punctures and durations of treatment and stay. Although this is a small, single-unit study with no statistical analysis, topic experts noted that the results may suggest that users of the NICE guideline may be having difficulty in determining which babies should be investigated and treated for infection.

However, the topic experts further stated that there is a need to reinforce the correct interpretation and implementation of the guideline (for example the word 'consider' does not mandate an action) rather than reword the guideline. Therefore no impact on the guideline is expected.

**Maternal group B streptococcus status to guide the decision on timing of delivery in women with preterm premature rupture of membranes**

We selected the secondary analysis of 2 randomised controlled trials (RCT) by Tajik et al. (2014) for a full commentary because it was highlighted by topic experts, and it examines management options for women with PPROM that are not currently discussed in NICE’s guideline on neonatal infection.

**What the guideline recommends**

NICE’s guideline on neonatal infection recommends that intrapartum antibiotic prophylaxis should be considered in women with PPROM, but no mention is made of assessing their group B streptococcus colonisation status, or considering immediate or delayed delivery based on this status.
NICE's guideline on **inducing labour** recommends that 'If a woman has PPROM after 34 weeks, the maternity team should discuss the following factors with her before a decision is made about whether to induce labour: risks to the woman (for example, sepsis, possible need for caesarean section); risks to the baby (for example, sepsis, problems relating to preterm birth).'

NICE's guideline on **preterm labour and birth** makes recommendations on identifying infection in women with PPROM, but does not discuss testing for group B streptococcus colonisation or using colonisation status to make decisions on timing of delivery.

**Methods**

The secondary analysis of 2 RCTs by Tajik et al. (2014) investigated whether women with vaginal group B streptococcus colonisation and PPROM would benefit from immediate delivery versus expectant management. The 2 RCTs included 723 women across 60 hospitals in the Netherlands with a singleton or twin pregnancy between 34 and 37 weeks of gestation who were not in labour 24 hours after PPROM. Participants were randomised to immediate delivery (labour induced within 48 hours, or caesarean delivery if vaginal delivery was contraindicated) or expectant management (monitoring based on local protocol until onset of spontaneous delivery). In the expectant management group, labour was induced if the pregnancy reached 37+0 weeks, or could be induced before this if clinically necessary (such as for infection). Most women were managed as inpatients but some centres allowed outpatient management. Antepartum and intrapartum antibiotics were given according to local protocols.

The primary outcome of the original RCTs was early-onset neonatal sepsis. This was defined as a positive blood culture taken at birth (not *Staphylococcus epidermidis*) or, within 72 hours, 2 or more symptoms of infection (apnoea, temperature instability, lethargy, feeding intolerance, respiratory distress, haemodynamic instability) plus 1 of the following: (i) positive blood culture, (ii) CRP above 20 mmol/litre, or (iii) positive surface cultures of a known virulent pathogen. The primary aim of this secondary analysis was whether immediate delivery benefited women with PPROM and vaginal group B streptococcus colonisation based on a logistic regression model. All analyses were intention-to-treat.

**Results**

In the original RCTs, immediate delivery did not significantly reduce the risk of early-onset neonatal sepsis compared with expectant management. In this analysis, when only women with vaginal group B streptococcus colonisation (14% of participants) were considered, the risk of neonatal sepsis was significantly lower with immediate delivery than expectant management: odds ratio=0.10 (95% [CI] 0.01 to 0.84). However in women without colonisation, the risk of neonatal
Sepsis did not differ significantly between the immediate delivery and expectant management groups: odds ratio = 1.16 (95% CI 0.44 to 3.03). When these odds ratios were compared, a significant difference was observed between the effect of immediate delivery in colonised and uncolonised women (p = 0.04). Namely, that immediate delivery appeared to reduce the risk of early-onset neonatal sepsis in women with PPROM who also had vaginal group B streptococcus colonisation.

**Strengths and limitations**

**Strengths**

- The analysis was based on data from 2 multicentre RCTs.

**Limitations**

- The study authors acknowledged that this was a secondary analysis not pre-specified in the trial protocols. Therefore, they stated that findings should be validated before applying to clinical practice.

- Antibiotics were given according to local protocols which introduced variability across study centres. Antibiotic use was also found to differ between groups, but antibiotics were not factored into the analysis.

- Group B streptococcus colonisation status was based only on vaginal swab (no anal swabs were taken), which may have underestimated the number of carriers. Additionally, for some patients, vaginal swabs were obtained during admission and not at study entry.

- No protocol for uniform specimen handling was used, and the media used for culturing samples to identify group B streptococcus varied across participating centres.

- The original RCTs and this analysis were not powered to detect differences in rare outcomes such as maternal sepsis.

- Implementing the findings of the study would require group B streptococcus screening to be introduced in a subset of women, but health economic data and impact on health services and patients were not considered.
Impact on guideline

The evidence suggests that women with PPROM between 34 and 37 weeks' gestation might benefit from immediate delivery if they have group B streptococcus vaginal colonisation, while in non-colonised women labour induction could be delayed until 37 weeks.

NICE's guideline on neonatal infection currently recommends that intrapartum antibiotic prophylaxis should be considered in women with PPROM, but no mention is made of assessing their group B streptococcus colonisation status, or considering immediate or delayed delivery based on this status. Screening is out of scope for this guideline, and topic experts noted that changing recommendations in this area would amount to starting a screening campaign in a subset of women with PPROM.

The UK National Screening Committee recommends that screening for group B streptococcus should not be offered to all pregnant women. However this recommendation is related to informing a decision about whether to give intrapartum antibiotic prophylaxis, rather than any other intervention such as immediate or delayed delivery. Additionally, no recommendations are made about screening within subgroups, such as women with PPROM. As the new evidence relates to assessing a subgroup (and is therefore not considered population screening), it may therefore be appropriate to consider making NICE recommendations based on this evidence.

Other guidelines may also be affected by this evidence. NICE's guideline on inducing labour makes recommendations on the decision whether to induce labour in women with PPROM after 34 weeks, including consideration of sepsis risk in the baby. Additionally, NICE's guideline on preterm labour and birth makes recommendations on identifying infection in women with PPROM, but does not discuss testing for group B streptococcus colonisation or using colonisation status to make decisions on timing of delivery. Consideration of the impact of the evidence for these guidelines may be appropriate, though limitations of the evidence (particularly that it is a post-hoc analysis with no consideration of costs) should be taken into account.
How we made the decision

We check our guidelines regularly to ensure they remain up to date. We based the decision on surveillance 4 years after the publication of neonatal infection (early onset) (2012) NICE guideline CG149.

For details of the process and update decisions that are available, see ensuring that published guidelines are current and accurate in 'Developing NICE guidelines: the manual'.

Previous surveillance update decisions for the guideline are on our website.

New evidence

We found 52 new studies in a search for systematic reviews, randomised controlled trials and observational studies published between 1 January 2014 and 9 March 2016.

Evidence identified in previous surveillance 2 years after publication of the guideline was also considered. This included 5 studies identified by search.

From all sources, 57 studies were considered to be relevant to the guideline.

We also checked for relevant ongoing research, which will be evaluated again at the next surveillance review of the guideline.

See appendix A: summary of new evidence from surveillance and references for all new evidence considered.

Views of topic experts

We considered the views of topic experts, including those who helped to develop the guideline and other correspondence we have received since the publication of the guideline. This included a meeting with experts to discuss potential areas for update.

Views of stakeholders

Stakeholders are consulted only if we decide not to update the guideline following checks at 4 and 8 years after publication. Because this was a 4-year surveillance review, and the decision was to update, we did not consult on the decision.
See ensuring that published guidelines are current and accurate in 'Developing NICE guidelines: the manual' for more details on our consultation processes.

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