4-year surveillance (2017)

Neonatal infection (early onset) (2012) NICE guideline CG149

Appendix A: Summary of new evidence from surveillance

Information and support

149 – 01	**What information and support should be provided for parents and carers?**

Notes

The review protocol for this question noted: 'The Guideline Committee may also consider evidence from studies reporting the views or experiences of women who were offered intrapartum antibiotics or whose babies were offered antibiotic prophylaxis or treatment.'

Recommendations derived from this question

1.1.1.1 If clinical concerns about possible early-onset neonatal infection arise during pregnancy or in the first 72 hours after birth (for example, in relation to risk factors [see table 1 in section 1.2.1] or clinical indicators [see table 2 in section 1.2.1]):

- tell the baby's parents and carers
- explain the reason for concern (including the nature of early-onset neonatal infection)
- discuss the preferred options for management (for example, observation, investigations or antibiotic treatment)
- give the baby's parents and carers time to consider the information provided, and offer further opportunities for discussion if necessary.

1.1.1.2 If considering antibiotic treatment because of clinical concerns about possible early-onset neonatal infection, discuss:

- the rationale for the treatment
- the risks and benefits in the individual circumstances
- the observations and investigations that may be needed to guide clinical management (for example, when to stop treatment)
- the preferred antibiotic regimen and likely duration of treatment
- the impact, if any, on where the woman or her baby will be cared for.

1.1.1.3 To maintain communication with a woman in labour whose baby is at increased risk of infection, healthcare professionals should involve the woman in any handover of care, either when additional expertise is brought in because of the risk of infection or during planned changes in staff. The handover should include an update about the presence of any infection. [This recommendation is adapted from recommendation 1.3.2 in Intrapartum care (NICE clinical guideline 55).]

1.1.1.4 Reassure parents and carers that they will be able to continue caring for, and holding, their baby according to their wishes unless the baby is too ill to allow this. If the severity of the baby's illness means they need to change the way they care for the baby, discuss this with them.

1.1.1.5 Reassure parents and carers that babies at increased risk of, or with, early-onset neonatal infection can usually continue to breastfeed, and that every effort will be made to facilitate

this. If a baby is temporarily unable to breastfeed, support the mother to express breast milk if she wishes to do so.

1.1.1.6 If the woman had group B streptococcal colonisation in a previous pregnancy but without infection in the baby, reassure her that this will not affect the management of the birth in the current pregnancy.

1.1.1.7 Offer parents and carers contact details of organisations that provide parent support, befriending, counselling, information and advocacy. They may signpost families to other sources of help. [This recommendation is adapted from recommendation 1.5.2 in Bacterial meningitis and meningococcal septicaemia (NICE clinical guideline 102).]

1.1.1.8 If there have been any concerns about early-onset neonatal infection before a baby is discharged, advise the parents and carers verbally and in writing that they should seek medical advice (for example, from NHS Direct, their general practice, or an accident and emergency department) if they are concerned that the baby:

- is showing abnormal behaviour (for example, inconsolable crying or listlessness), or
- is unusually floppy, or
- has developed difficulties with feeding or with tolerating feeds, or
- has an abnormal temperature unexplained by environmental factors (lower than 36°C or higher than 38°C), or
- has rapid breathing, or
- has a change in skin colour.

1.1.1.9 When the baby is discharged from the hospital or midwifery-led unit (or in the immediate postnatal period in the case of babies born at home), inform the parents and carers and the baby's GP, verbally and in writing, if the baby is considered to be at increased risk of infection.

1.1.1.10 If a baby has been treated for suspected or confirmed early-onset neonatal infection:

- inform the parents and carers about potential long-term effects of the baby's illness and likely patterns of recovery, and reassure them if no problems are anticipated
- take account of parents' and carers' concerns when providing information and planning follow-up.

1.1.1.11 When a baby who has had a group B streptococcal infection is discharged from hospital:

- advise the woman that if she becomes pregnant again:
  - there will be an increased risk of early-onset neonatal infection
  - she should inform her maternity care team that a previous baby has had a group B streptococcal infection
  - antibiotics in labour will be recommended
- inform the woman's GP in writing that there is a risk of:
  - recurrence of group B streptococcal infection in the baby, and
  - group B streptococcal infection in babies in future pregnancies.

1.1.1.12 If the woman has had group B streptococcal colonisation in the pregnancy but without infection in the baby, inform her that if she becomes pregnant again, this will not affect the management of the birth in the next pregnancy.

1.1.1.13 For every baby about whom there has been a clinical concern regarding early-onset neonatal infection, formulate a post-discharge management plan, taking into account factors such as:

- the level of the initial clinical concern
- the presence of risk factors
- parents' and carers' concerns.

Surveillance decision

This review question should not be updated.

Parental consent in neonatal antibiotic use

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance summary
An opinion piece[1] by a midwife entitled 'Who safeguards mothers?' noted that pregnant women found to be carrying group B streptococcus, but who decline intravenous antibiotics for themselves in labour, can seek support from midwives. But once the woman's baby is born, the situation - such as the legal context – changes, and the issue of safeguarding may be raised. The article considers the issues that arise in such scenarios and raises questions about who is there to support women who experience pressure to consent to their healthy newborn baby having prophylactic intravenous antibiotics.

Topic expert feedback
The Association for Improvements in the Maternity Services (AIMS) raised the issue of parents questioning the use of prophylactic antibiotics in special care baby units. They noted that the ability of parents to raise questions of concern to them varies with the atmosphere and communication patterns in different units, and queries to the AIMS helpline suggests considerable variation in this. They explained that in some cases, queries to healthcare professionals may be being met with an 'authoritarian response', likely out of concern for vulnerable neonates. They raised concerns that such responses may adversely affect any future communication with healthcare professionals.

Other intelligence gathering indicated that the general principles of consent in neonates is covered in the British Association of Perinatal Medicine document 'Consent in neonatal clinical care: Good practice framework', although this has existed for a long time and was likely considered when this guideline was developed.

The legal framework for consent in all patients is covered in the Department of Health guidance 'Reference guide to consent for examination or treatment (second edition)', but again this has existed for many years and is already referenced in guidelines.

Impact statement
No evidence was identified to inform this review question in the original guideline. The full guideline notes that in the absence of evidence, the Guideline Committee based its recommendations on the knowledge and experience of its members, emphasising that 'the ethos of the entire guideline was to promote informed choice for parents and carers of babies at increased risk of early-onset neonatal infection or with suspected or confirmed early-onset neonatal infection'. Several recommendations were made in CG149, including that: preferred management options should be discussed with parents and carers; time and opportunities to consider and discuss information should be given; risks and benefits should be explained; and details of organisations that can provide support, befriending, counselling, information and advocacy should be offered. The concerns raised by the recent evidence and expert feedback may therefore reflect implementation issues rather than omissions from the guideline. CG149 already recommends that management options should be discussed with parents and carers and that appropriate support is provided.

New evidence is unlikely to change guideline recommendations.

Risk factors for infection and clinical indicators of possible infection

149 – 02	**Which maternal and fetal risk factors for early-onset neonatal infection/sepsis should be used to guide management?**

Recommendations derived from this question

1.2.1 Recognising risk factors and clinical indicators

1.2.1.1 Use table 1 to identify risk factors for early-onset neonatal infection and table 2 to identify clinical indicators of early-onset neonatal infection.

1.2.1.2 Use tables 1 and 2 to identify red flags (risk factors and clinical indicators that should prompt a high level of concern regarding early-onset neonatal infection).

Table 1 Risk factors for early-onset neonatal infection, including 'red flags'

Risk factor	Red flag
Invasive group B streptococcal infection in a previous baby	
Maternal group B streptococcal colonisation, bacteriuria or infection in the current pregnancy	
Prelabour rupture of membranes	
Preterm birth following spontaneous labour (before 37 weeks' gestation)	
Suspected or confirmed rupture of membranes for more than 18 hours in a preterm birth	
Intrapartum fever higher than 38°C, or confirmed or suspected chorioamnionitis	
Parenteral antibiotic treatment given to the woman for confirmed or suspected invasive bacterial infection (such as septicaemia) at any time during labour, or in the 24-hour periods before and after the birth [This does not refer to intrapartum antibiotic prophylaxis]	Yes
Suspected or confirmed infection in another baby in the case of a multiple pregnancy	Yes

Table 2 Clinical indicators of possible early-onset neonatal infection (observations and events in the baby), including 'red flags'

Risk factor	Red flag
Altered behaviour or responsiveness	
Altered muscle tone (for example, floppiness)	
Feeding difficulties (for example, feed refusal)	
Feed intolerance, including vomiting, excessive gastric aspirates and abdominal distension	
Abnormal heart rate (bradycardia or tachycardia)	
Signs of respiratory distress	

Respiratory distress starting more than 4 hours after birth	Yes
Hypoxia (for example, central cyanosis or reduced oxygen saturation level)	
Jaundice within 24 hours of birth	
Apnoea	
Signs of neonatal encephalopathy	
Seizures	Yes
Need for cardio–pulmonary resuscitation	
Need for mechanical ventilation in a preterm baby	
Need for mechanical ventilation in a term baby	Yes
Persistent fetal circulation (persistent pulmonary hypertension)	
Temperature abnormality (lower than 36°C or higher than 38°C) unexplained by environmental factors	
Signs of shock	Yes
Unexplained excessive bleeding, thrombocytopenia, or abnormal coagulation (International Normalised Ratio greater than 2.0)	
Oliguria persisting beyond 24 hours after birth	
Altered glucose homeostasis (hypoglycaemia or hyperglycaemia)	
Metabolic acidosis (base deficit of 10 mmol/litre or greater)	
Local signs of infection (for example, affecting the skin or eye)	

1.2.2 Before the birth

1.2.2.1 For women in labour identify and assess any risk factors for early-onset neonatal infection (see table 1). Throughout labour monitor for the emergence of new risk factors, such as intrapartum fever higher than 38°C, or the development of chorioamnionitis.

1.2.2.2 Manage prelabour rupture of membranes at term according to the recommendations in Intrapartum care (NICE clinical guideline 55).

1.2.3 After the birth

1.2.3.1 If there are any risk factors for early-onset neonatal infection (see table 1) or if there are clinical indicators of possible early-onset neonatal infection (see table 2) perform a careful clinical assessment without delay. Review the maternal and neonatal history and carry out a physical examination of the baby including an assessment of the vital signs.

1.2.3.2 Use the following framework based on risk factors and clinical indicators, including red flags (see tables 1 and 2), to direct antibiotic management decisions:

- In babies with any red flags, or with two or more 'non-red flag' risk factors or clinical indicators (see tables 1 and 2), perform investigations (see recommendations 1.5.1.1–1.5.1.3) and start antibiotic treatment. Do not delay starting antibiotics pending the test results (see recommendations 1.6.1.1–1.6.1.3).

- In babies without red flags and only one risk factor or one clinical indicator, using clinical judgement, consider:
  - whether it is safe to withhold antibiotics, and
  - whether it is necessary to monitor the baby's vital signs and clinical condition – if monitoring is required continue it for at least 12 hours (at 0, 1 and 2 hours and then 2-hourly for 10 hours).

Surveillance decision

This review question should be updated.

Maternal obesity

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance review
A study[2] of full-term pregnancies among 109,488 women using data from the Consortium of Safe Labor study (collected electronic medical records in 228,562 deliveries from 19 hospitals) examined neonatal morbidities among infants born to obese mothers. Of the women in the study, 18% were obese. 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 those of normal-weight women.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The new evidence indicates that maternal obesity may be a risk factor for neonatal sepsis in full-term newborns. Obesity is not currently stated to be a risk factor in CG149.

New evidence identified that may change current recommendations.

Rupture of membranes

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance summary
A systematic review and meta-analysis[3] of 122 studies (7 studies from very high neonatal mortality settings) examined the prevalence of early-onset neonatal infection among newborns of mothers with risk factors related to rupture of membranes. The prevalence of early-onset neonatal laboratory-confirmed infection among infants born to mothers with prelabour rupture of membranes, preterm prelabour rupture of membranes, or prolonged rupture of membranes was 3–19% depending on the risk factor.

An observational, epidemiological population-based cohort study[4] evaluated the effect of preterm prelabour rupture of membranes as a cause of preterm delivery on significant morbidities in 4120 very-low-birth-weight infants less than 32 weeks' gestation. Preterm prelabour rupture of membranes as the cause of preterm delivery had no independent effect on the risk of early-onset sepsis, clinical sepsis and blood-culture proven sepsis, while gestational age proved to be the most important contributor to sepsis risk.

Topic expert feedback
Topic experts noted that 1 of the studies[4] looked only at babies less than 32 weeks' gestation who already have a risk factor because they are premature. It was also noted that changing this area of the guideline could have a significant impact on UK practice, but (as several experts noted) the study[4] was at high risk of bias and so may not be of sufficient quality to warrant any review.

Impact statement
Only 1 moderate quality cohort study (n=462) in the original guideline provided specific evidence in this area, and was for prolonged preterm prelabour rupture of membranes. The Guideline Committee noted however that in fact no evidence was identified that directly answered the review question, and so used its own knowledge and experience to formulate recommendations.

The new evidence indicates that neonatal infection has been observed in the presence of prelabour (term and preterm) and prolonged rupture of membranes, which is consistent with CG149 that notes these as risk factors. Additionally, gestational age was found to contribute to sepsis risk, which is consistent with CG149 in that preterm birth before 37 weeks' gestation is noted as a risk factor.

However there is also evidence that in very-low-birth-weight infants less than 32 weeks' gestation, preterm prelabour rupture of membranes as the cause of preterm delivery had no independent effect on the risk of early-onset sepsis, clinical sepsis and blood-culture proven sepsis. This is potentially in conflict with CG149 which notes that preterm prelabour rupture of membranes is a risk factor for early-onset infection. As no evidence in the original guideline specifically informed this recommendation, there may be an impact on the guideline. However the authors noted a number of limitations of their study and that population-based registry data do not constitute conclusive evidence. Topic experts noted that the risk of bias was such that the evidence may not warrant any changes, and that 79% had caesarean section which reduces sepsis risk therefore the evidence is difficult to interpret. Additionally experts noted that the study included only premature babies – these babies are already noted by CG149 to be at risk of infection and the current risk factors are satisfactory.

New evidence is unlikely to change guideline recommendations.

Epidural anaesthesia

2-year Evidence Update
A retrospective cohort study[5] (n=960) investigated whether epidural anaesthesia was a risk factor for neonatal fever. Epidural anaesthesia was an independent risk factor for neonatal fever, both in all mother–infant pairs and in pairs where the mother did not have fever, but was not associated with a higher incidence of neonatal infection.

4-year surveillance summary
A study[6] examined whether neonatal sepsis is mediated by maternal fever in women undergoing epidural analgesia in labour. Women delivering with epidural analgesia were matched with 453 women delivering without epidural analgesia. Significantly more neonates born in the epidural analgesia-group had fever at birth. The overall incidence of proven or suspected neonatal sepsis was significantly higher in the epidural analgesia group but the incidence of proven neonatal sepsis alone was not. Epidural analgesia was an independent risk factor for neonatal sepsis. However, in the epidural analgesia group as well as the non-epidural analgesia group, the incidence of neonatal sepsis was significantly higher in mothers with intrapartum fever compared with afebrile mothers. The authors concluded that the positive association between neonatal sepsis and labour epidural analgesia is possibly mediated by maternal intrapartum fever.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The 2-year Evidence Update found that epidural anaesthesia was an independent risk factor for neonatal fever, but not sepsis. It concluded that in infants with fever whose mothers had epidural anaesthesia, and in the presence of no other risk factors or clinical features of neonatal infection, observation is appropriate instead of investigations and treatment for sepsis. The evidence was, however, deemed unlikely to have an impact on CG149 given the small numbers of infants (n=34) with fever in the study.

At the 4-year surveillance review, although the evidence found that epidural analgesia was an independent risk factor for neonatal sepsis, it also found that incidence of sepsis was significantly higher in febrile than afebrile mothers. The authors therefore concluded that

the link between neonatal sepsis and epidural analgesia was possibly mediated by maternal intrapartum fever. This evidence is consistent with CG149 that states intrapartum fever is a risk-factor for early-onset neonatal infection.

New evidence is unlikely to change guideline recommendations.

Chorioamnionitis

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance summary
Six studies evaluated the effect of chorioamnionitis on neonatal infection:

- A study[7] of 281 preterm infants less than 32 weeks' gestational age found chorioamnionitis was significantly associated with early onset sepsis.
- A multicentre retrospective analysis[8] examined prospectively collected data on 8,330 very-low-birth-weight infants less than 32 weeks' gestational age, of whom 1,480 (18%) were exposed to chorioamnionitis. After adjusting for confounding factors, infants exposed to chorioamnionitis had a significantly higher risk of early-onset neonatal sepsis.
- An observational study[9] of 451 very-low-birth-weight neonates, of whom 31 (7%) were exposed to chorioamnionitis found (after correcting for gestational age and birth weight) chorioamnionitis was significantly associated with early-onset neonatal sepsis.
- A study[10] of 99 women with singleton pregnancies complicated by preterm prelabour rupture of membranes between the gestational ages of 34–37 weeks found that women with both microbial invasion of the amniotic cavity and acute histologic chorioamnionitis had the significantly highest incidence of newborns with early-onset sepsis.
- A study[11] of 395 preterm neonates with birth weight of up to 1,500 g, of whom 100 (25%) had probable or confirmed early-onset neonatal sepsis, found a significantly greater incidence of sepsis in infants with chorioamnionitis.
- A multicentre, prospective surveillance study[12] examined whether chorioamnionitis-exposed newborns with culture-confirmed early-onset infection can be asymptomatic at birth. Of 396,586 live births, records for 229 chorioamnionitis-exposed neonates with early-onset infection were reviewed: 29 (13%) had no documented symptoms within 6 hours of birth, including 21 (9%) who remained asymptomatic at 72 hours. The authors concluded that some infants born to mothers with chorioamnionitis may have no signs of sepsis at birth despite having culture-confirmed infections.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The new evidence indicates that chorioamnionitis is significantly associated with early-onset sepsis, which is consistent with CG149 that states confirmed or suspected chorioamnionitis is a risk-factor for early-onset neonatal infection.

The evidence also suggests that infants exposed to chorioamnionitis and with culture-confirmed infection may have no signs of sepsis at birth. This is consistent with recommendations in CG149 that an array of maternal, fetal and neonatal risk factors and clinical indicators, and continued monitoring, should direct antibiotic management decisions.

New evidence is unlikely to change guideline recommendations.

Maternal colonisation and infection

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance summary
A prospective cohort study[13] of 1,694 term infants determined whether maternal group B streptococcus colonisation was associated with an increased risk of infants needing to be transferred to the neonatal intensive care unit. A total of 26% of mothers were colonised, and infants born to colonised mothers were significantly more likely to be transferred to intensive care than infants of non-colonised mothers.

An exploratory UK national case-control study[14] (n=30 women with confirmed or suspected severe group B streptococcus sepsis, and 757 controls) estimated the incidence of severe maternal sepsis due to group B streptococcus, and investigated associated outcomes for mother and infant. The incidences of confirmed and presumed severe maternal group B streptococcal sepsis were 1.00 and 2.75 per 100,000 maternities, respectively, giving an overall incidence of 3.75 per 100,000. Compared with controls, severe maternal group B streptococcal sepsis was associated with higher odds of infant sepsis.

A systematic review and meta-analysis[3] of 122 studies (7 studies from very high neonatal mortality settings) examined the prevalence of early-onset neonatal infection among newborns of mothers with bacterial infection or colonisation (bacteria not specified). The prevalence of early-onset neonatal laboratory-confirmed infection among newborns was 17% for mothers with laboratory-confirmed infection, and 0% for colonised mothers.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
Evidence indicates that maternal colonisation with group B streptococcus is associated with adverse neonatal outcomes serious enough to warrant intensive care. Further evidence also found that severe maternal sepsis due to group B streptococcus is associated with increased risk of neonatal sepsis, and more generally, 17% of infants born to mothers with infection develop early-onset infection. This is consistent with CG149 that states maternal group B streptococcal colonisation, bacteriuria or infection in the current pregnancy is a risk-factor for early-onset neonatal infection.

New evidence is unlikely to change guideline recommendations.

Various risk factors

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance review
A prediction model[15] based on data from 970 women obtained from 2 recent RCTs on induction of labour versus expectant management in late preterm prelabour rupture of membranes evaluated whether neonatal sepsis can be predicted from antepartum parameters. A total of 13 potential antepartum predictors for neonatal sepsis were evaluated. Thirty-three (3%) neonates suffered neonatal sepsis. Maternal age (per year), maternal C-reactive protein level (per mmol/l), maternal temperature (per degree C) and positive group B streptococcus culture were associated with a significantly increased risk of neonatal sepsis.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
Increased maternal temperature and positive group B streptococcus culture are already noted in CG149 as risk factors for neonatal infection. Although maternal age and maternal C-reactive protein level are not currently mentioned as risk factors in CG149, the women in the study all had preterm prelabour rupture of membranes which is already recognised as a risk factor in the guideline.

New evidence is unlikely to change guideline recommendations.

Maternal group B streptococcus antibodies

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance review
A prospective, multicentre, case-control study[16] (n=33 mothers delivering neonates with early onset group B streptococcal infection, and 99 age- and ethnicity-matched controls colonised with the same group B streptococcus types) examined if maternal antibodies can prevent early-onset group B streptococcal disease. For group B streptococcus types Ia and III, maternal concentrations of type Ia- and type IIIa-specific antibody greater than 0.5 micrograms/ml were significantly associated with a 90% risk reduction for neonatal infection. For group B streptococcus type V, maternal concentrations of type V-specific antibody greater than 0.5 micrograms/ml were non-significantly associated with a 70% risk reduction for neonatal infection. By Bayesian modeling, the risk of early onset disease would decrease by 70% if maternal specific antibody concentrations for these 3 group B streptococcus types were greater than 1 microgram/ml.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
Although the new evidence indicates that high concentrations of maternal antibodies against group B streptococcus may protect against neonatal infection (which is not currently discussed by CG149), further research from larger studies is needed to confirm the results.

New evidence is unlikely to change guideline recommendations.

Fetal splenic vein flow pattern

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance review
A study[17] of 129 women with singleton pregnancies and preterm prelabour rupture of membranes between 24and 36 weeks' gestation assessed neonatal outcome against the pulsatile fetal splenic vein flow pattern. Doppler evaluation of the fetal splenic vein flow was performed. The flow-velocity waveform pattern was evaluated qualitatively as continuous or pulsatile. Pulsatile splenic vein flow was associated with a significantly higher rate of early-onset neonatal sepsis.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
Although the new evidence indicates that pulsatile splenic vein flow is associated with neonatal sepsis (which is not currently discussed by CG149), further research from larger studies is needed to confirm the results.

New evidence is unlikely to change guideline recommendations.

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149 – 03 **Which risk factors in the baby (including symptoms and signs) should raise suspicion of infection/sepsis within 72 hours of birth?**

Recommendations derived from this question

1.2.1 Recognising risk factors and clinical indicators

1.2.1.1 Use table 1 to identify risk factors for early-onset neonatal infection and table 2 to identify clinical indicators of early-onset neonatal infection.

1.2.1.2 Use tables 1 and 2 to identify red flags (risk factors and clinical indicators that should prompt a high level of concern regarding early-onset neonatal infection).

1.2.3 After the birth

1.2.3.1 If there are any risk factors for early-onset neonatal infection (see table 1) or if there are clinical indicators of possible early-onset neonatal infection (see table 2) perform a careful clinical assessment without delay. Review the maternal and neonatal history and carry out a physical examination of the baby including an assessment of the vital signs.

1.2.3.2 Use the following framework based on risk factors and clinical indicators, including red flags (see tables 1 and 2), to direct antibiotic management decisions:

- In babies with any red flags, or with two or more 'non-red flag' risk factors or clinical indicators (see tables 1 and 2), perform investigations (see recommendations 1.5.1.1–1.5.1.3) and start antibiotic treatment. Do not delay starting antibiotics pending the test results (see recommendations 1.6.1.1–1.6.1.3).
- In babies without red flags and only one risk factor or one clinical indicator, using clinical judgement, consider:
  - whether it is safe to withhold antibiotics, and
  - whether it is necessary to monitor the baby's vital signs and clinical condition – if monitoring is required continue it for at least 12 hours (at 0, 1 and 2 hours and then 2-hourly for 10 hours).

1.2.3.3 In babies being monitored for possible infection:

- if clinical concern increases, consider performing necessary investigations (see recommendations 1.5.1.1–1.5.1.3) and starting antibiotic treatment (see recommendations 1.6.1.1–1.6.1.3)
- if no further concerns arise during the period of observation reassure the family and, if the baby is to be discharged, give advice to the parents and carers (see recommendation 1.1.1.8).

1.2.3.4 If a baby needs antibiotic treatment it should be given as soon as possible and always within 1 hour of the decision to treat.

1.2.3.5 Manage suspected bacterial meningitis according to the recommendations in Bacterial meningitis and meningococcal septicaemia (NICE clinical guideline 102) unless the baby is already receiving care in a neonatal unit.

1.2.3.6 Manage suspected urinary tract infection according to the recommendations in Urinary tract infection in children (NICE clinical guideline 54).

1.2.3.7 Continue routine postnatal care (see Postnatal care, NICE clinical guideline 37) for babies without risk factors (see table 1) or clinical indicators of possible infection (see table 2).

1.2.3.8 If maternal colonisation with group B streptococcus is first identified after the birth but within the first 72 hours of life, ask the person directly involved in the baby's care (for example, a parent, carer or healthcare professional) whether they have any concerns, identify any other risk factors present and look for clinical indicators of infection. Use this assessment to decide on clinical management (see recommendation 1.2.3.2).

Surveillance decision

This review question should not be updated.

Neonatal risk factors combined with maternal risk factors

2-year Evidence Update

No relevant evidence was identified.

4-year surveillance review

A retrospective nested case-control study[18] aimed to define a quantitative stratification algorithm for the risk of early-onset sepsis in newborns greater than 34 weeks' gestation. Data collected on each infant included sepsis risk at birth based on objective maternal factors, demographics, specific clinical milestones, and vital signs during the first 24 hours after birth. Using a combination of recursive partitioning and logistic regression, a

risk classification scheme was developed for early-onset sepsis in the derivation dataset. This scheme was then applied to the validation dataset. Using a base population of 608,014 live births greater than 34 weeks' gestation at 14 hospitals, all 350 cases of early-onset sepsis were identified and frequency matched by hospital and year of birth to 1063 controls. Using maternal data (obtained from a previous study by the same authors) and neonatal data, a risk stratification scheme was defined that divided the neonatal population into 3 groups: treat empirically, observe and evaluate, and continued observation (see table below).

<table>
<tr><td></td><td colspan="3">Sepsis risk at birth estimated from maternal risk factors (gestational age, group B streptococcus status, rupture of membranes time, intrapartum temperature, intrapartum antibiotics treatment)</td></tr>
<tr><td>Neonatal clinical presentation</td><td><0.65/1000 live births</td><td>0.65–1.54/1000 live births</td><td>≥1.54/1000 live births</td></tr>
<tr><td>Well appearing
The infant did not fall into one of the below 2 groups in the first 12 h of age</td><td>CONTINUED OBSERVATION
85% of live births
NNT=9,370</td><td>OBSERVE AND EVALUATE
11% of live births
NNT=823</td><td rowspan="3">TREAT EMPIRICALLY
4% of live births
NNT=118</td></tr>
<tr><td>Equivocal presentation
In the first 12h of age, the infant experienced at least 2 instances of 1 of the following, with ‘instance’ meaning that there were ≥2 measurements ≥2h apart:
- Heart rate ≥160
- Respiratory rate ≥60
- Temperature ≥100.4°F (38°C) or <97.5°F (36.4°C)
- Respiratory distress (grunting, flaring, or retracting)</td><td>OBSERVE AND EVALUATE
11% of live births
NNT=823</td><td></td></tr>
<tr><td>Clinical illness
In the first 12h of age, the infant had a 5-min Apgar <5; received nasal continuous positive airway pressure or mechanical ventilation; received continuous infusion of vasoactive drugs; had a clinical seizure; or had significant respiratory distress (nasal flaring, grunting, or retractions were present and the infant received supplemental oxygen within the first 6h)</td><td colspan="2"></td></tr>
</table>

Topic expert feedback

The topic experts stated that the above study may provide a more sound evidence-based basis for the risk factors given in CG149.

Impact statement

All of the maternal and neonatal risk factors identified by the authors that should contribute to decisions on the management of infants at risk of early-onset infection are already noted as risk factors by CG149, however this study may provide additional evidence to support the use of these risk factors.

New evidence is unlikely to change guideline recommendations.

Intrapartum antibiotics

149 – 04	**What is the effectiveness of intrapartum antibiotic prophylaxis in the prevention of early-onset neonatal infection (compared to no treatment)?**

Recommendations derived from this question

1.3.1.1 Offer intrapartum antibiotic prophylaxis using intravenous benzylpenicillin to prevent early-onset neonatal infection for women who have had:

- a previous baby with an invasive group B streptococcal infection
- group B streptococcal colonisation, bacteriuria or infection in the current pregnancy.

1.3.1.2 If the woman decides to take intrapartum antibiotic prophylaxis, give the first dose as soon as possible and continue prophylaxis until the birth of the baby.

1.3.1.3 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.

1.3.1.4 Consider intrapartum antibiotic prophylaxis using intravenous benzylpenicillin to prevent early-onset neonatal infection for women in preterm labour if there is suspected or confirmed intrapartum rupture of membranes lasting more than 18 hours.

1.3.1.5 Offer benzylpenicillin as the first choice for intrapartum antibiotic prophylaxis. If the woman is allergic to penicillin, offer clindamycin unless individual group B streptococcus sensitivity results or local microbiological surveillance data indicate a different antibiotic.

Surveillance decision

This review question should be updated.

Intrapartum antibiotic prophylaxis in women with preterm prelabour rupture of membranes

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance summary
No relevant evidence was identified.

Topic expert feedback
Topic experts highlighted a 2014 audit of current practice in preventing early-onset neonatal group B streptococcal disease by the Royal College of Obstetricians and Gynaecologists. The audit aimed to:

- Investigate the implementation of the Royal College's Green Top Guideline (GTG) 36 (2012) 'Group B Streptococcal Disease, Early-onset' in NHS maternity units.
- Examine variation in preventive care.
- Identify areas for improving adherence to GTG36 and preventive care.

The audit report found that at least one respondent in 41.2% of units reported that group B streptococcus-specific intrapartum antibiotic prophylaxis was offered to women with preterm prelabour rupture of membranes. The Royal College does not recommend this course of action (GTG36 section 6.4 states: '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.')

Instead, according to GTG44 (2010) 'Preterm Prelabour Rupture of Membranes', these women should have received prophylactic antibiotics for 10 days after diagnosis of preterm prelabour rupture of membranes.

However, the audit noted that NICE CG149 recommends consideration of intrapartum antibiotic prophylaxis for this group. The audit report stated: 'It is a concern that there is a discrepancy between GTG44 and CG149 that intrapartum antibiotic prophylaxis for early-onset neonatal infections should be considered for women with preterm prelabour rupture of membranes'.

Impact statement
Regarding whether intrapartum antibiotic prophylaxis should be offered to women with preterm prelabour rupture of membranes: there is disagreement between the Royal College and NICE, and the new evidence indicates that that local practice is split. These issues may warrant further investigation.

New evidence identified that may change current recommendations.

Efficacy of intrapartum antibiotic prophylaxis

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance summary
A Cochrane review[19] of 4 RCTs (n=852) examined intrapartum antibiotic prophylaxis for known maternal group B streptococcal colonisation. The use of intrapartum antibiotic prophylaxis versus no treatment did not significantly reduce the incidence of all-cause neonatal mortality, or neonatal mortality from infection caused by group B streptococcus or other bacteria. The incidence of early-onset group B streptococcal infection was significantly reduced with intrapartum antibiotic prophylaxis compared to no treatment, though the authors noted a high risk of bias for one or more key domains in the methodology and execution of the single study contributing to this result. The incidence of late-onset disease or sepsis from organisms other than group B streptococcus was not significantly different between groups. No significant difference was seen in neonatal or maternal outcomes for intrapartum ampicillin versus penicillin.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The new evidence indicates that early-onset group B streptococcal infection was significantly reduced with intrapartum antibiotic prophylaxis, which is consistent with CG149 that it should be offered to all women with group B streptococcal colonisation. Additionally, all 4 RCTs identified by this Cochrane review were included in the original guideline.

New evidence is unlikely to change guideline recommendations.

Adding an intrapartum polymerase chain reaction (PCR) test for group B streptococcus to a risk-based intrapartum antibiotic prophylaxis strategy

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance summary
A 2-phase study[20] investigated if an automated real-time PCR-assay (Xpert GBS), used bedside by labour ward personnel, was manageable and could decrease the use of intrapartum antibiotic prophylaxis in a setting with a risk-based intrapartum antibiotic prophylaxis strategy. Phase 1 of the study was a multicentre RCT (n=229). Women with selected risk-factors were allocated either to PCR-intrapartum antibiotic prophylaxis (prophylaxis given if positive or indeterminate) or intrapartum antibiotic prophylaxis without PCR. Excluding indeterminate results, the assay showed a sensitivity of 89% and a specificity of 90% compared with bacterial culture as the reference standard. In 44% of the PCR assays the result was indeterminate. The use of intrapartum antibiotic prophylaxis was significantly lower in the PCR group. Phase 2 (n=94) was a non-randomised assessment of an improved version of the assay in which the proportion of indeterminate results was reduced (15%).

NICE medtech innovation briefing 28 commented on this study and noted in a discussion of its limitations that 'The primary eligibility criteria [included] […] selected obstetric risk factors for group B streptococcus, but these were not the same as the risk factors used in the UK and this introduces issues of generalisability.'

In the product summary and likely place in therapy, the briefing noted: 'If a rapid and effective test to detect group B streptococcus colonisation were adopted, it could improve antibiotic stewardship. The Xpert GBS test could be used to identify group B streptococcus colonisation at the onset of labour as an adjunct to the risk factor-based approach, and could potentially reduce the unnecessary use of intrapartum antibiotic prophylaxis.'

A study[21] examined the clinical performance of an isothermal recombinase polymerase amplification assay for detecting group B streptococci in vaginal/anal samples from 50 pregnant women in labour. The limit of detection and the analytical specificity of the isothermal assay were also compared to real-time PCR. Compared to real-time PCR, the recombinase polymerase amplification assay showed a clinical sensitivity of 96% and a clinical specificity of 100%. The limit of detection was 98 genome copies and the analytical specificity was 100% for a panel of 15 bacterial and/or fungal strains naturally found in the vaginal/anal flora. Time-to-result for the recombinase polymerase amplification assay was less than 20 minutes compared to 45 minutes for the real-time PCR assay; a positive sample could be detected as early as 8 minutes.

Topic expert feedback
The topic experts noted that there is an ongoing HTA-funded study (due to publish May 2018) examining the accuracy of the Xpert GBS test for maternal group B streptococcal colonisation and its potential to reduce antibiotic usage in mothers with risk factors.

Impact statement
Currently the guideline states that intrapartum antibiotic prophylaxis should be offered to women who have had a previous baby with an invasive group B streptococcal infection, or group B streptococcal colonisation, bacteriuria or infection in the current pregnancy. No recommendations are made about ad hoc intrapartum testing or screening for maternal group B streptococcal colonisation to supplement decisions about giving antibiotics. The new evidence for the Xpert GBS real-time PCR test indicates it could be used alongside a risk-based strategy to reduce the number of women who receive intrapartum antibiotic prophylaxis. However, the study did not assess any outcomes related to sepsis or any other neonatal adverse outcomes, nor did it assess costs. Results from the HTA-funded study are anticipated (which alongside rates of maternal intrapartum antibiotic prophylaxis, will look at maternal and neonatal morbidity and mortality, and relative cost-effectiveness of the strategies).

Evidence for the isothermal recombinase polymerase amplification assay suggests it could provide a faster but similarly accurate alternative to real-time PCR testing for group B streptococcus. However without evidence of its effect on antibiotic use or patient outcomes, or any cost data, firm conclusions cannot be made.

New evidence is unlikely to change guideline recommendations.

Intrapartum antibiotic prophylaxis guided by either routine culture-based screening or risk-based management

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance summary
A systematic review and meta-analysis[22] of 8 comparative cohort studies (with historical or concurrent control groups) and 1 quasi experimental study compared intrapartum antibiotic prophylaxis guided by either routine culture-based screening or risk-based management for the prevention of early-onset group B streptococcus disease. In a meta-analysis of combined term and preterm infants, neonates of mothers exposed to the routine culture-based protocol had significantly less chance of developing early-onset group B streptococcus disease than those whose mothers were managed by a risk-based strategy. A similarly significant benefit of the

culture-based protocol was seen in an analysis of term infants only. Preterm infants were 4 times more likely to develop early-onset group B streptococcus disease than term infants regardless of prevention technique (with neither technique significantly better than other). One study provided information on neonatal mortality in which there was 1 neonatal death in the risk-based cohort and none in the culture-based. The rate of administration of intrapartum antibiotic prophylaxis was significantly greater in women exposed to the culture-based protocol than those exposed to the risk-based protocol. The authors noted that the review was limited by the low level of evidence available on this topic and that higher-level evidence such as RCTs is needed.

Topic expert feedback
The topic experts noted that there is an updated National Screening Committee review on group B Streptococcus screening in pregnancy due in 2017. They indicated that it is going through final changes and would publish soon.

Impact statement
The new evidence indicates that intrapartum antibiotic prophylaxis guided by routine culture-based screening was associated with less neonatal group B streptococcus disease than a risk-based strategy. Although CG149 recommends a risk-based approach, the limited quality of the evidence is unlikely to affect this. Additionally, antenatal screening and antibiotic prophylaxis for bacterial infections are out of scope for CG149, and covered by CG62 Antenatal care (though a research recommendation in CG149 asks 'What is the clinical and cost effectiveness of intrapartum antibiotic prophylaxis targeting group B streptococcus and guided by routine antenatal screening?' It notes the research could take the form of health economic modelling.) The new evidence does not discuss costs.

NICE does not normally make screening recommendations as this is not within its remit and the UK National Screening Committee is deferred to.

New evidence is unlikely to change guideline recommendations.

Intrapartum antibiotic prophylaxis for women with meconium-stained amniotic fluid

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance summary
A Cochrane review[23] of 2 RCTs (n=362 women) assessed intrapartum antibiotic prophylaxis for meconium-stained amniotic fluid in preventing maternal and neonatal infections. Both studies compared ampicillin-sulbactam with normal saline. Prophylactic antibiotics did not significantly reduce the incidence of neonatal sepsis. No serious adverse effects were reported. Most of the domains for risk of bias were at low risk of bias for one study and at unclear risk of bias for the other study. The quality of the evidence using GRADE was low for neonatal sepsis.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The study authors concluded that there was no evidence that antibiotics for meconium-stained amniotic fluid in labour could reduce neonatal sepsis. This is consistent with the following statement in the full guideline: 'The Guideline Committee's view was that there was no evidence to support intrapartum antibiotics [for meconium-stained amniotic fluid] for the benefit of the baby. The Committee also noted that it is not usual obstetric practice to offer antibiotic treatment to women for meconium-stained amniotic fluid. Therefore, the Guideline Committee made no recommendation for this group of women.'

New evidence is unlikely to change guideline recommendations.

Avoiding routine use of antibiotics in the baby

149 – 05	**In babies with maternal risk factors for early-onset neonatal infection is routine administration of antibiotics to the baby effective in preventing early-onset neonatal infection?**

Recommendations derived from this question

1.4.1.1 Do not routinely give antibiotic treatment to babies without risk factors for infection or clinical indicators or laboratory evidence of possible infection.

Surveillance decision

This review question should not be updated.

Routine antibiotic prophylaxis in asymptomatic neonates with known risk factors

2-year Evidence Update

No relevant evidence was identified.

4-year surveillance review

A systematic review[24] of 3 RCTs examined the effects of prophylactic treatment of asymptomatic neonates less than 7 days old with known risk factors for early-onset group B streptococcal infection. The review was split into 3 sections. The first section examined early antibiotic prophylaxis versus monitoring and selective antibiotics treatment in asymptomatic infants born to mothers with risk factors for neonatal infection. Two RCTs (n=166) were included. For effect on infection, 1 RCT had no events therefore effect size was inestimable, and the other found no significant difference between interventions. For mortality, no events occurred in either trial. The second section examined early antibiotic prophylaxis versus monitoring and selective antibiotic treatment in low-birthweight, preterm infants. One RCT (n=1187) was included in this section, in which no significant difference between interventions was seen for either infection or mortality. The third section intended to compare different antibiotics for routine antibiotic prophylaxis for group B streptococcal infection, but no studies were found.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

In asymptomatic neonates with risk factors, the new evidence could not firmly establish whether routine antibiotic prophylaxis is more effective than monitoring and selective antibiotic treatment at reducing the incidence of early-onset group B streptococcal infections or reducing mortality. Additionally, routine antibiotic prophylaxis seems no more effective than monitoring and selective antibiotic treatment at reducing the incidence of early-onset group B streptococcal infections or reducing mortality. The evidence is consistent with CG149 to base antibiotic initiation on assessment of risk factors and continued monitoring.

New evidence is unlikely to change guideline recommendations.

Investigations before starting antibiotics in the baby

149 – 06	**What investigations of asymptomatic babies after birth are useful in identifying those who should/not be treated for early-onset neonatal infection or determining the treatment strategy?**
149 – 07	**What investigations should be performed prior to commencing treatment in:** **- babies with symptoms** **- babies with risk factors without symptoms?**

Recommendations derived from these questions

1.5.1.1 When starting antibiotic treatment in babies with risk factors for infection or clinical indicators of possible infection, perform a blood culture before administering the first dose.

1.5.1.2 Measure the C-reactive protein concentration at presentation when starting antibiotic treatment in babies with risk factors for infection or clinical indicators of possible infection.

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.

If performing the lumbar puncture would unduly delay starting antibiotics, perform it as soon as possible after starting antibiotics.

1.5.1.4 Do not routinely perform urine microscopy or culture as part of the investigation for early-onset neonatal infection.

1.5.1.5 Do not perform skin swab microscopy or culture as part of the investigation for early-onset neonatal infection in the absence of clinical signs of a localised infection.

1.5.1.6 Be aware that, although minor conjunctivitis with encrusting of the eyelids is common and often benign, a purulent discharge may indicate the presence of a serious infection (for example, with chlamydia or gonococcus).

1.5.1.7 In babies with a purulent eye discharge take swab samples urgently for microbiological investigation, using methods that can detect chlamydia and gonococcus. Start systemic antibiotic treatment for possible gonococcal infection while awaiting the swab microbiology results.

1.5.1.8 In babies with clinical signs of umbilical infection, such as a purulent discharge or signs of periumbilical cellulitis (for example, redness, increased skin warmth or swelling), perform a blood culture, take a swab sample for microscopy and culture, and start antibiotic treatment with intravenous flucloxacillin and gentamicin (see recommendation 1.6.1.3)[a]. If the microbiology results indicate that the infection is not due to a Gram-negative infection, stop the gentamicin.

a Gentamicin is licensed for use in newborn babies. The summary of product characteristics recommends a dosage of 4–7 mg/kg/day administered in a single dose. The evidence reviewed for the guideline supports a starting dosage of 5 mg/kg every 36 hours administered in a single dose.

Surveillance decision

This review question should not be updated.

Full blood count

2-year Evidence Update

A retrospective cohort study[25] evaluated the accuracy of full blood count in diagnosing early-onset infection in neonates admitted to 293 US neonatal intensive care units over a 13 year period (n=166,092 neonates with 171,376 cultures). The sensitivity of the blood count indices for early-onset infection was low, with the highest sensitivity observed for an immature to total neutrophil ratio (I:T ratio) of more than 0.24 (49%). Specificity was generally higher, with the lowest specificity for an absolute neutrophil count of less than 4134/mm^3 (74%). The positive likelihood ratios ranged from 1.5 for a platelet count of less than 147,000/mm^3, to 2.5 for an I:T ratio of more than 0.24. The negative likelihood ratios ranged from 0.6 for an I:T ratio of more than 0.24, to 1 for a platelet count of less than 147,000/mm^3. The Evidence Update concluded that full blood count indices may not be sufficiently sensitive to rule out early-onset infection in neonates

4-year surveillance review

A study[26] of infants born at greater than 35 weeks' gestation investigated the impact of implementing a protocol aiming at reducing the number of diagnostic tests in infants with risk factors for early-onset sepsis in order to compare the diagnostic performance of repeated clinical examination with full blood count and C-reactive protein measurement. Two time periods were compared, before and after the change of screening protocol.

Period 1: Full blood count and C-reactive protein measured in all infants born to mothers with at least 1 risk factor (inadequate group B streptococcus prophylaxis, rupture of membranes more than 18 hours, maternal fever, less than 37 weeks' gestation). No instructions given about timing of diagnostic tests. Vital signs checked by midwives every 4 hours during the first 24 hours and every 8 hours during the next 24 hours in all infants with risk factors. Period 2: In addition to midwives monitoring vital signs, infants with risk factors were examined by paediatric residents every 8 hours during the first 24 hours. Full blood count performed only in infants exposed to chorioamnionitis. During the 2 study periods, starting antibiotics was at the discretion of the attending neonatologist and blood cultures were obtained only in treated patients. Blood cultures, full blood counts and C-reactive protein measurements were performed during the 2 study periods in all treated patients to help determine duration of antibiotics. Lumbar punctures were performed on an individual basis and urine cultures were not part of the diagnostic workup.

Among the 11,503 infants included, 222 were treated with antibiotics for suspected early-onset sepsis. The proportion of infants receiving antibiotics for suspected sepsis before and after the change of protocol did not differ significantly. Reduction of diagnostic tests was associated with significantly earlier antibiotic treatment in infants treated for suspected sepsis, and in infants with neonatal infection. There was no difference in the duration of hospital stay nor in the proportion of infants requiring respiratory or cardiovascular support before and after the change of protocol.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

The Evidence Update found that full blood count indices may not be sufficiently sensitive to rule out early-onset infection in neonates. This was deemed unlikely to impact the guideline, as it does not make recommendations on full blood count for the diagnosis of early-onset neonatal infection.

Evidence from the 4-year surveillance found that reduction of diagnostic tests (as per period 2 of the study) such as full blood count and C-reactive protein does not delay initiation of antibiotic treatment in infants with suspected early-onset sepsis, and reinforced the value of clinical examination in infants with risk factors for early-onset sepsis. Period 2 of the study is consistent with practice already recommended in CG149, namely that: chorioamnionitis is a risk factor; in lower risk babies, clinical judgement should be used to consider whether it is safe to withhold antibiotics, and whether it is necessary to monitor the baby's vital signs and clinical condition; blood cultures and C-reactive protein measurements were performed in all treated patients to help determine duration of antibiotics; lumbar punctures were performed on an individual basis; and urine cultures were not part of the diagnostic workup. The evidence is not fully applicable as it includes full blood counts which CG149 does not include recommendations on.

New evidence is unlikely to change guideline recommendations.

Procalcitonin

2-year Evidence Update
A meta-analysis[27] of 16 cohort and case–control studies (n=1959) assessed the value of serum procalcitonin for the diagnosis of early-onset neonatal infection. The sensitivity was 81%, the specificity was 79%, the positive likelihood ratio was 3.9 and the negative likelihood ratio was 0.24. The heterogeneity of the evidence (I^2=96%) prevented firm conclusions.

4-year surveillance review
No relevant evidence was identified.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
In the original guideline, the Guideline Committee considered that procalcitonin assessments were insufficiently useful to accurately rule in or rule out early-onset neonatal infection in babies about to start antibiotic treatment and chose not to recommend the use of these tests.

The Evidence Update deemed the evidence unlikely to have an impact on CG149, which does not include any recommendations on using serum procalcitonin as a diagnostic marker.

New evidence is unlikely to change guideline recommendations.

PCR assays

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance review
A study[28] examined the Xpert GBS real-time PCR assay for rapid detection of group B streptococcus in gastric fluid samples from 143 newborns. The assay detected group B streptococcus within 1 hour for 16 (11%) cases, while microscopic examination detected only 2 cases. The sensitivity and specificity of the assay were 80% and 100% respectively, with regard to 20 cases of group B streptococcus colonisation or infection. The concordance of Xpert GBS results with culture was 92%.

Topic expert feedback
Topic experts noted that COGNITOR is a PCR test done on blood culture bottles at 12 hours, and is reported to have a very high negative predictive value. It seems to offer a real opportunity to assist in the assessment of babies at 36 hours or earlier, in that it would overcome difficulties in getting a negative blood culture result after 36 hours incubation. It has the added advantage that it is done on the blood culture, so doesn't involve collecting more blood from babies. The experts felt that additional research in this area would help inform the guideline in the future.

COGNITOR was not considered for inclusion in NICE DG20 'Tests for rapidly identifying bloodstream bacteria and fungi (LightCycler SeptiFast Test MGRADE, SepsiTest and IRIDICA BAC BSI assay)' because the scope was designed to focus on technologies for which no prior incubation of blood culture was necessary, that is PCR could be done directly on the blood sample. Tests that could be run directly on whole blood have the potential to speed up the pathogen identification process in critically ill patients, where rapid decisions are needed.

Impact statement
In the original guideline, 1 of 3 studies that evaluated the diagnostic test accuracy of PCR found it to be a very useful test for ruling in and ruling out early-onset neonatal infection. The inconsistency of the findings between studies, concerns with the level of PCR in preterm and term babies, and the cost of performing the test led the Guideline Committee to conclude that it should not be recommended.

The new evidence indicates that the Xpert GBS real-time PCR assay may have promise in diagnosing sepsis faster than blood culture.

COGNITOR is another PCR test that may also offer a faster diagnosis than standard blood culture.

The recommendation in NICE DG20 was 'There is currently insufficient evidence to recommend the routine adoption in the NHS of the LightCycler SeptiFast Test MGRADE, SepsiTest and IRIDICA BAC BSI assay for rapidly identifying bloodstream bacteria and fungi. The tests show promise and further research to provide robust evidence is encouraged'. CG149 does not currently include recommendations on any form of PCR testing to diagnose neonatal infection, though NICE has recommended PCR tests in other guidance on infectious disease. For example, CG102 Meningitis recommendation 1.3.8: 'Perform whole blood real-time PCR testing (EDTA sample) for N meningitidis to confirm a diagnosis of meningococcal disease.'

Further evidence is awaited for rapid PCR testing of blood samples for diagnosing neonatal infection.

New evidence is unlikely to change guideline recommendations.

Calprotectin

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance review
A study[29] of 41 infants who underwent blood culture for suspected sepsis investigated serum calprotectin as a potential biomarker for sepsis. Serum calprotectin was measured by ELISA assay. Sepsis was culture-proven in 8 neonates (20%) and suspected in 33 (80%). The optimal cut-off for calprotectin was 2.2 micrograms/ml with a sensitivity of 63% and a specificity of 70%.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The study provides evidence of the potential of calprotectin as a biomarker for sepsis. CG149 does not currently include recommendations on use of this biomarker, however the small size of the study means the evidence is unlikely to have an impact.

New evidence is unlikely to change guideline recommendations.

Interleukins

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance review
A systematic review and meta-analysis[30] of 6 studies examined the accuracy of serum interleukin-6 in sepsis diagnosis. In a subgroup analysis of neonates, interleukin-6 had a pooled sensitivity of 77% and specificity of 91% for sepsis diagnosis.

A systematic review and meta-analysis[31] of 8 studies (n=548 neonates) examined serum interleukin-8 for diagnosis of neonatal sepsis. The pooled sensitivity and specificity of interleukin-8 were 0.78 and 0.84 respectively. The pooled diagnostic odds ratio was 21.64 and area under the curve was 0.8908. The diagnostic threshold analysis showed that there was no threshold effect. Funnel plots showed the existence of publication bias.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The first meta-analysis showed moderate sensitivity and higher specificity of interleukin-6 for diagnosing sepsis. The authors of the second meta-analysis concluded that interleukin-8 had a moderate accuracy for the diagnosis of neonatal sepsis and is a helpful biomarker for early diagnosis of neonatal sepsis. However, they stated that results should be combined with clinical symptoms and signs, laboratory and microbial results.

In the original guideline, the Guideline Committee considered 4 studies and concluded that interleukin (6, 8 and 10) assessments were insufficiently useful to accurately rule in or rule out early-onset neonatal infection in babies

about to start antibiotic treatment and chose not to recommend the use of these tests.

Although the new evidence shows some promise, there remains no clear evidence that interleukin tests could be used on their own to rule in or rule out neonatal infection.

New evidence is unlikely to change guideline recommendations.

Mannose-binding lectin

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance review
A systematic review and meta-analysis[32] of 7 studies examined low mannose-binding lectin levels and mannose-binding lectin genetic polymorphisms associated with the risk of neonatal sepsis. The pooled unadjusted odds ratio showed that low mannose-binding lectin levels were significantly associated with neonatal sepsis and mannose-binding lectin genetic polymorphisms were also significantly associated with neonatal sepsis. In a subgroup analysis based on gestational age, significantly increased risk was found in the preterm infants in the dominant model. However, no association was observed for term infants in subgroup analysis. Additionally, the summary receiver operating characteristic curve of low mannose-binding lectin levels in the prediction of neonatal sepsis indicated a poor predictive ability. The area under curve was 0.80.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The authors concluded that a low serum mannose-binding lectin level was only of moderate value in detecting neonatal sepsis, therefore this evidence is unlikely to impact CG149 which does not include recommendations on mannose-binding lectin as a sepsis biomarker.

New evidence is unlikely to change guideline recommendations.

Tumour necrosis factor-alpha

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance review
A systematic review and meta-analysis[33] of 23 trials examined tumour necrosis factor-alpha as a diagnostic marker for neonatal sepsis. Tumour necrosis factor-alpha showed moderate accuracy in diagnosing early-onset neonatal sepsis (sensitivity=0.66, specificity=0.76). It was also found that the northern hemisphere group in the test had higher sensitivity (0.84) and specificity (0.83).

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The moderate accuracy of tumour necrosis factor-alpha in diagnosing neonatal sepsis is unlikely to impact CG149 which does not include recommendations on use of this biomarker.

New evidence is unlikely to change guideline recommendations.

Neutrophil CD64

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance review
A study[34] examined the diagnostic accuracy and prognostic value of the neutrophil CD64 expression index in 129 very low birth weight neonates as a marker of early-onset sepsis. The highest performance of the CD64 index was achieved at 24 hours after birth with a cut-off value of 2.4: accuracy=0.85, sensitivity=0.89, and negative predictive value=0.99. The increased expression of CD64

index was significantly associated with subsequent infections.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The neutrophil CD64 expression index appears to be a potentially useful marker of neonatal sepsis. CG149 does not currently include recommendations on use of this biomarker, however the study was relatively small and further evidence is needed before considering for inclusion in the guideline.

New evidence is unlikely to change guideline recommendations.

CD14 subtype (presepsin)

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance review
A study[35] of 65 critically ill full-term and preterm newborns admitted to the neonatal intensive care unit examined the diagnostic accuracy of soluble CD14 subtype (also called presepsin) in diagnosing neonatal bacterial sepsis and in discriminating non-bacterial systemic inflammatory response syndrome from bacterial sepsis. Of the 65 newborns, 25 had bacterial sepsis, 15 had non-bacterial systemic inflammatory response syndrome with no localising source of bacterial infection, and 25 had no infection. Blood presepsin levels were significantly higher in bacterial sepsis when compared with controls. However, no significant difference was found between bacterial sepsis and non-bacterial systemic inflammatory response syndrome. C-reactive protein and presepsin did not correlate with each other; presepsin had an area under the curve significantly greater than that of C-reactive protein.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
Presepsin may be a potentially useful marker of neonatal sepsis. CG149 does not currently include recommendations on use of this biomarker, however the study was relatively small and further evidence is needed on the diagnostic ability (sensitivity, specificity, likelihood ratios, predictive values).

New evidence is unlikely to change guideline recommendations.

Chest radiography

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance review
No relevant evidence was identified.

Topic expert feedback
A topic expert reported that pneumonia is a common presentation of early-onset neonatal sepsis, and may be missed if a chest radiograph is not performed. Group B streptococcal pneumonia mimics respiratory distress syndrome (Ablow 1977), and should be considered if a baby with radiographic appearances of respiratory distress syndrome is disproportionately sick.

The NICE guideline does not give a directive on the role of chest radiography as part of a screen for early-onset neonatal sepsis, however it is notable that even in older children pneumonia may be present with limited clinical signs, and there is significant added value of chest radiography in the diagnosis of pneumonia (Ayalon 2013).

Impact statement
No new evidence was found by surveillance to support the topic expert view and this area will be evaluated again at the next surveillance review.

New evidence is unlikely to change guideline recommendations.

Antibiotics for suspected infection

149 – 08	**What is the optimal antibiotic treatment regimen for suspected early-onset neonatal infection?**

Recommendations derived from this question

1.6.1.1 Use intravenous benzylpenicillin with gentamicin as the first-choice antibiotic regimen for empirical treatment of suspected infection unless microbiological surveillance data reveal local bacterial resistance patterns indicating a different antibiotic.

1.6.1.2 Give benzylpenicillin in a dosage of 25 mg/kg every 12 hours[a]. Consider shortening the dose interval to 8-hourly based on clinical judgement (for example, if the baby appears very ill).

1.6.1.3 Give gentamicin in a starting dosage of 5 mg/kg[b].

1.6.1.4 If a second dose of gentamicin is to be given (see recommendation 1.7.2.1) it should usually be given 36 hours after the first dose. The interval may be shortened, based on clinical judgement, for example if:

- the baby appears very ill
- the blood culture shows a Gram-negative infection.

1.6.1.5 Decide on subsequent gentamicin doses and intervals taking account of blood gentamicin concentrations (see recommendations 1.8.1.1–1.8.2.3).

1.6.1.6 Record the times of:

- gentamicin administration
- sampling for therapeutic monitoring.

1.6.1.7 Regularly reassess the clinical condition and results of investigations in babies receiving antibiotics. Consider whether to change the antibiotic regimen taking account of:

- the baby's clinical condition (for example, if there is no improvement)
- the results of microbiological investigations
- expert microbiological advice, taking account of local surveillance data.

1.6.1.8 If there is microbiological evidence of Gram-negative bacterial sepsis, add another antibiotic to the benzylpenicillin and gentamicin regimen that is active against Gram-negative bacteria (for example, cefotaxime). If Gram-negative infection is confirmed stop benzylpenicillin.

a Benzylpenicillin is licensed for use in newborn babies. The summary of product characteristics recommends a dosage of 50 mg/kg/day in two divided doses in babies under 1 week of age. In babies aged 1–4 weeks the dosage should be increased to 75 mg/kg/day in three divided doses, as recommended in the summary of product characteristics.

b Gentamicin is licensed for use in newborn babies. The summary of product characteristics recommends a dosage of 4–7 mg/kg/day administered in a single dose. The evidence reviewed for the guideline supports a starting dosage of 5 mg/kg every 36 hours administered in a single dose.

Surveillance decision

This review question should not be updated.

Gentamicin dosing

2-year Evidence Update

A retrospective observational study[36] (n=33) evaluated an extended interval dosing regimen of gentamicin in preterm infants with a gestational age of 28 weeks or less who received gentamicin for suspected sepsis for at least 5 days. A first 5 mg/kg dose of gentamicin was given on the first day of life. The timing of the second 5 mg/kg dose was based on gentamicin level at 22 hours:

- 1.2 micrograms/ml or less=second dose at 24 hours
- 1.3–2.6 micrograms/ml=second dose at 36 hours
- 2.7–3.5 micrograms/ml=second dose at 48 hours
- 3.6 micrograms/ml or more=hold next dose and repeat measurement of gentamicin level at 24 hours. Base dosing interval on time to achieve a level of less than 2 micrograms/ml.

Among the 33 neonates, 20 received gentamicin at 36-hour intervals and 13 at 48-hour intervals. The majority (91%) achieved the target peak (5–12 micrograms/ml) and trough (less than 2 micrograms/ml) levels of gentamicin, with no significant difference between the 36-hour and 48-hour interval groups.

4-year surveillance review
No relevant evidence was identified.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The 2-year Evidence Update concluded that a dosing regimen of 5 mg/kg gentamicin every 36 or 48 hours according to blood gentamicin levels at 22 hours can achieve effective and safe peak and trough levels of gentamicin in very preterm babies, but this was unlikely to impact CG149 given that it recommends considering a 5 mg/kg dose of gentamicin every 36 hours in term and preterm infants.

New evidence is unlikely to change guideline recommendations.

Antibiotic resistance

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance review
No relevant evidence was identified.

Topic expert feedback
The topic experts noted that since the guideline was written, the proportion of Gram-negative bacteria that are resistant to gentamicin has increased. Although the majority of these bacteria remain gentamicin sensitive, the following might be considered: a) advising that neonatologists review antibiotic susceptibility data (in line with NICE NG15 Antimicrobial stewardship) and/or b) include a statement along the lines of 'gentamicin-resistant Gram-negative bacilli are an uncommon cause of early-onset neonatal sepsis, but should be considered in patients who deteriorate despite initiation of empiric antibiotics.'

Impact statement
The NICE pathway for Antibiotics for early-onset neonatal infection cross-links to the NICE pathway for Antimicrobial stewardship. Additionally, CG149 recommendation 1.6.1.1 states: 'Use intravenous benzylpenicillin with gentamicin as the first-choice antibiotic regimen for empirical treatment of suspected infection unless microbiological surveillance data reveal local bacterial resistance patterns indicating a different antibiotic.' And recommendation 1.6.1.7 states: 'Consider whether to change the antibiotic regimen taking account of: the results of microbiological investigations; and expert microbiological advice, taking account of local surveillance data'. No impact on the guideline is therefore anticipated.

New evidence is unlikely to change guideline recommendations.

Duration of antibiotic treatment

149 – 09 **What is the optimal duration (or course length) of antibiotics for babies:**
- with confirmed early-onset neonatal infection (bacterial cause identified)
- with presumed symptomatic infection but no bacterial cause identified
- with initial clinical suspicion of infection but no ongoing clinical concerns and all investigations normal
- asymptomatic babies receiving prophylactic treatment?

Recommendations derived from this question

1.7.1 Investigations during antibiotic treatment

1.7.1.1 In babies given antibiotics because of risk factors for infection or clinical indicators of possible infection, measure the C-reactive protein concentration 18–24 hours after presentation.

1.7.1.2 Consider performing a lumbar puncture to obtain a cerebrospinal fluid sample 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 C-reactive protein concentration of 10 mg/litre or greater, or
- has a positive blood culture, or
- does not respond satisfactorily to antibiotic treatment.

1.7.2 Decisions 36 hours after starting antibiotic treatment

1.7.2.1 In babies given antibiotics because of risk factors for infection or clinical indicators of possible infection, consider 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 C-reactive protein concentration are reassuring.

1.7.2.2 Consider establishing hospital systems to provide blood culture results 36 hours after starting antibiotics to facilitate timely discontinuation of treatment and discharge from hospital.

1.7.2.3 Clinical microbiology or paediatric infectious disease advice should be available every day from healthcare professionals with specific experience in neonatal infection.

1.7.3 Early-onset neonatal infection without meningitis

1.7.3.1 The usual duration of antibiotic treatment for babies with a positive blood culture, and for those with a negative blood culture but in whom there has been strong suspicion of sepsis, should be 7 days. Consider continuing antibiotic treatment for more than 7 days if:

- the baby has not yet fully recovered, or
- this is advisable, based on the pathogen identified on blood culture (seek expert microbiological advice if necessary).

1.7.3.2 If continuing antibiotics for longer than 36 hours despite negative blood cultures, review the baby at least once every 24 hours. On each occasion, using clinical judgement, consider whether it is appropriate to stop antibiotic treatment, taking account of:

- the level of initial clinical suspicion of infection
- the baby's clinical progress and current condition, and

- the levels and trends of C-reactive protein concentration.

1.7.4 Meningitis (babies in neonatal units)

1.7.4.1 If a baby is in a neonatal unit and meningitis is suspected but the causative pathogen is unknown (for example, because the cerebrospinal fluid Gram stain is uninformative), treat with intravenous amoxicillin and cefotaxime.

1.7.4.2 If a baby is in a neonatal unit and meningitis is shown to be due to Gram-negative infection either by cerebrospinal fluid Gram stain or culture, stop amoxicillin and treat with cefotaxime alone.

1.7.4.3 If a baby is in a neonatal unit and meningitis is shown by cerebrospinal fluid Gram stain to be due to a Gram-positive infection, continue treatment with intravenous amoxicillin and cefotaxime while awaiting the cerebrospinal fluid culture result and seek expert microbiological advice.

1.7.4.4 If the cerebrospinal fluid culture is positive for group B streptococcus consider changing the antibiotic treatment to:

- benzylpenicillin 50 mg/kg every 12 hours[a], normally for at least 14 days, and
- gentamicin in a starting dosage of 5 mg/kg every 36 hours[b], with subsequent doses and intervals adjusted if necessary based on clinical judgement (see recommendation 1.6.1.4) and blood gentamicin concentrations (see recommendations 1.8.1.1–1.8.2.3); gentamicin treatment should continue for 5 days.

1.7.4.5 If the blood culture or cerebrospinal fluid culture is positive for listeria consider stopping cefotaxime and treating with amoxicillin and gentamicin.

1.7.4.6 If the cerebrospinal fluid culture identifies a Gram-positive bacterium other than group B streptococcus or listeria seek expert microbiological advice on management.

1.7.5 Discharge after antibiotic treatment

1.7.5.1 On completing antibiotic treatment, consider prompt discharge of the baby from hospital, with support for the parents and carers and a point of contact for advice.

a Benzylpenicillin is licensed for use in newborn babies. The summary of product characteristics recommends a dosage of 50 mg/kg/day in two divided doses in babies under 1 week of age. In babies aged 1–4 weeks the dosage should be increased to 75 mg/kg/day in three divided doses, as recommended in the summary of product characteristics.

b Gentamicin is licensed for use in newborn babies. The summary of product characteristics recommends a dosage of 4–7 mg/kg/day administered in a single dose. The evidence reviewed for the guideline supports a starting dosage of 5 mg/kg every 36 hours administered in a single dose.

Surveillance decision

This review question should not be updated.

C-reactive protein measurement to guide management

2-year Evidence Update

A retrospective cohort study[37] assessed the effect of consecutive testing of C-reactive protein concentration on duration of antibiotic use in preterm infants of very low birth weight with negative blood cultures during the first week postpartum. C-reactive protein concentration was measured at initial evaluation and at 48 hours. Antibiotic treatment should have been stopped within 48 hours in those with normal C-reactive protein values (<10 mg/litre) at both time points and a negative blood culture at 48 hours. Of 569 infants who received empiric antibiotics in the first week postpartum, antibiotics were: correctly discontinued at 48 hours in 311 infants with 2 normal C-reactive protein results; correctly continued in 98 infants with at least 1 elevated C-reactive protein concentration (>10 mg/litre); but non-compliantly continued for more than 48 hours in 160 infants with normal C-reactive protein results. Infants treated according to C-reactive protein levels received a significantly smaller total dose of ampicillin, and had a significantly lower mortality rate than infants not treated according to C-reactive protein values.

4-year surveillance review

A prospective cohort study[38] examined the value of a single C-reactive protein measurement at 18 hours of age to identify neonates where antibiotics started for possible early-onset sepsis could safely be discontinued. The study included 647 preterm (less than 35 weeks' gestation) and 555 late preterm (35–36 weeks' gestation) or term newborns with maternal and/or neonatal risk factors for early-onset sepsis. C-reactive protein levels were measured between 15–21 hours of age. There were 16, 107 and 1079 neonates with proven, possible and no early-onset sepsis respectively. Among the 645 neonates with an 18-hour C-reactive protein level less than 10 mg/litre, 1 had proven early-onset sepsis, 43 had possible early-onset sepsis and 601 (93%) were not infected. All neonates with possible or proven early-onset sepsis were either less than 35 weeks' gestation, symptomatic at the time of C-reactive protein assessment or remained on antibiotics because of maternal bacteraemia: they would therefore not be considered for discharge. There were 557 neonates with an 18-hour C-reactive protein level greater than 10 mg/litre. Of these, 15 had proven early-onset sepsis, 64 had possible early-onset sepsis, and 478 (86%) were not infected. Sensitivity and specificity of 18-hour C-reactive protein for proven or possible early-onset sepsis were 64% and 56% respectively. The negative predictive value was 93%, and the positive predictive value was 14%.

A before-and-after study[39] investigated the effect of NICE CG149 on the number of investigations, length of stay and duration of antibiotics. The particular focus of the study was the recommendation of a second C-reactive protein level measurement 18–24 hours after presentation, and to consider 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 C-reactive protein concentration of 10 mg/litre or greater; or has a positive blood culture; or does not respond satisfactorily to antibiotic treatment. Two time periods, before and after the guidance was published, were compared. After NICE guidance, fewer screened babies stayed less than 72 hours but more babies stayed longer than 5 days. The proportion of babies having repeat C-reactive protein measurements nearly doubled, and in more than half of babies, the repeat C-reactive protein measurements increased antibiotics and hospital stay. The number of lumbar punctures performed also increased. There were no positive blood cultures or lumbar puncture results.

Topic expert feedback

The topic experts noted that it was important to consider any study[38] that could lead to less antibiotic use. However experts noted a number of limitations of the study including that:

• The sensitivity and specificity of the 18-hour C-reactive protein test was low.

• 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. Further research would be needed to examine the role of blood cultures.

• 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).

• 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 C-reactive protein only.

• The diagnostic utility of 18-hour CRP in conjunction with other criteria for stopping antibiotics has not been validated in other studies.

The topic experts also noted that users of the guideline appear to be having difficulty in determining which babies should be investigated and treated for infection. They cited the study[39] discussed above claiming that since the publication of CG149, there have been increases in investigations, lumbar punctures and durations of treatment and stay).

The following response to this study was drafted by 3 Guideline Committee members but never submitted to the journal:

"Mukherjee and colleagues are not alone in their concern that NICE CG149 is having unintended effects. We suggest that some of the difficulties arise because:

1. The guideline may not have been applied in full. For example, the most common risk factor in this report was prolonged rupture of membranes. The risk factor in CG149 and CG55 (Intrapartum Care) is prelabour rupture of membranes. 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 (Bellieni 2013; Kawamura 1995).

2. The clinical discretion advocated in the guideline is not applied. For example, the authors appear to have interpreted recommendation 1.7.1.2 as mandating a lumbar puncture if the second CRP was greater than 10mg/litre. They 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: '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.'

The outcomes reported from this centre may not reflect the guideline but its implementation in a particular setting. We speculate that more support for implementation may be needed. The guideline is not designed to cover all situations. NICE explicitly uses action verbs such as 'consider' to indicate when the evidence is weak and when clinicians can (should) follow their own judgment.

Finally, we strongly encourage others to audit and review the application of the guidelines in their own units. Tools to support implementation and an audit tool are available on the NICE website."

The topic experts stated that there is a need to reinforce the correct understanding and implementation of the guideline (for example the word 'consider' does not mandate an action) rather than reword the guideline.

Impact statement

The evidence identified by the 2-year Evidence Update was deemed to support the recommendation in CG149 that closely-timed serial C-reactive protein measurements can be used to guide antibiotic treatment in infants at risk of early-onset neonatal infection, and to confirm the applicability of this approach in infants of very low birth weight.

The authors of the study[38] of the value of a single C-reactive protein measurement at 18 hours of age concluded that the duration of antibiotic treatment in neonates born beyond 34 weeks' gestation and asymptomatic at the time of C-reactive protein assessment could be potentially reduced with a diagnostic algorithm that includes a point-of-care 18-hour C-reactive protein measurement, and that elevated 18-hour C-reactive protein in isolation should not be used as a reason to prolong antibiotics. Whereas CG149 utilises a raised C-reactive protein measurement at this time point to inform a consideration whether to perform lumbar puncture rather than to directly inform (dis)continuing antibiotics. It is not until 36 hours after commencing antibiotics that the guideline recommends using levels and trends of C-reactive protein, 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 C-reactive protein test was low. It may not therefore be an appropriate measure to use in isolation for diagnostics or to decide antibiotic course length. The study also did not examine interpreting C-reactive protein tests in the context of blood culture results. Further research may be needed to examine the role of blood cultures.

Although the study showed the potential of a single 18-hour CRP test, which differs from current recommendations in CG149, limitations of the study and lack of validation of its findings mean that no impact is anticipated.

Additionally, although a study[39] has suggested some potential for confusion when interpreting the guideline (which may in turn have led to increases in investigations, lumbar punctures and durations of treatment and stay), topic experts felt there is a need to reinforce the correct interpretation and implementation of the guideline rather than reword recommendations.

Therefore no impact on the guideline is expected.	New evidence is unlikely to change guideline recommendations.

Therapeutic drug monitoring for gentamicin

149 – 10	**What is the optimal drug monitoring strategy to achieve effective and safe antibiotic concentrations of gentamicin in the blood in babies with early-onset neonatal infection?**

Recommendations derived from this question

1.8.1 Trough concentrations

1.8.1.1 If a second dose of gentamicin is to be given (see recommendation 1.6.1.4) measure the trough blood gentamicin concentration immediately before giving the second dose. Consider the trough concentration before giving a third dose of gentamicin.

1.8.1.2 Hospital services should make blood gentamicin concentrations available to healthcare professionals in time to inform the next dosage decision (for example, within 30 hours of sampling).

1.8.1.3 Consider repeating the measurement of trough concentrations immediately before every third dose of gentamicin, or more frequently if necessary (for example, if there has been concern about previous trough concentrations or renal function).

1.8.1.4 Adjust the gentamicin dose interval, aiming to achieve trough concentrations of less than 2 mg/litre. If the course of gentamicin lasts more than three doses a trough concentration of less than 1 mg/litre is advised.

1.8.1.5 If an intended trough concentration measurement is not available, do not withhold the next dose of gentamicin unless there is evidence of renal dysfunction (for example, an elevated serum urea or creatinine concentration, or anuria).

1.8.2 Peak concentrations

1.8.2.1 Consider measuring peak blood gentamicin concentrations in selected babies such as in those with:

- oedema
- macrosomia (birthweight more than 4.5 kg)
- an unsatisfactory response to treatment
- proven Gram-negative infection.

1.8.2.2 Measure peak concentrations 1 hour after starting the gentamicin infusion.

1.8.2.3 If a baby has a Gram-negative or staphylococcal infection, consider increasing the dose of gentamicin if the peak concentration is less than 8 mg/litre.

Surveillance decision

No new information was identified at any surveillance review.

Care setting

149 – 11	**How does the choice of care setting impact on the clinical management of early-onset neonatal infection?**

Recommendations derived from this question

1.9.1.1 Using clinical judgement, consider completing a course of intravenous antibiotics outside of hospital (for example, at home or through visits to a midwifery-led unit) in babies who are well without ongoing concerns if there is adequate local support.

1.9.1.2 When deciding on the appropriate care setting for a baby, take into account the baby's clinical needs and the competencies necessary to ensure safe and effective care (for example, the insertion and care of intravenous cannulas).

Surveillance decision

No new information was identified at any surveillance review.

NQ – 01	**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?**

This question was not addressed by the guideline.

Surveillance decision

This question should be added.

Immediate delivery versus expectant management in women with preterm prelabour rupture of membranes and vaginal group B streptococcus colonisation

2-year Evidence Update

No relevant evidence was identified.

4-year surveillance summary

A secondary analysis[40] of 2 RCTs (n=723 women across 60 hospitals) investigated whether women with vaginal group B streptococcus colonisation and preterm prelabour rupture of membranes between 34and 37 weeks' gestation would benefit from immediate delivery versus expectant management. Antepartum and intrapartum antibiotics were given according to local protocols. Vaginal group B streptococcus colonisation was observed in 14% of women, and colonisation was significantly associated with benefit of immediate delivery. The risk of early-onset neonatal sepsis in group B streptococcus-positive women was significantly lower with immediate delivery than expectant management. Early onset neonatal sepsis risk was low in neonates of group B streptococcus-negative women in both the expectant management and immediate delivery groups. The authors estimated that by inducing labour only in group B streptococcus-positive women, there would be a 10% increase in term delivery rate, while keeping neonatal sepsis and caesarean delivery rates comparable to a strategy of labour induction for all.

Topic expert feedback

The topic experts cited the study above. They noted that in women with preterm prelabour rupture of membranes, those with group B streptococcus vaginal colonisation might

benefit from immediate delivery, while in group B streptococcus-negative women, delaying induction may be preferable, as it may reduce early-onset neonatal infection in the baby.

Topic experts noted some issues with the study, including that it was a post hoc study, intrapartum antibiotics were variable but not considered by the analysis, vaginal swabs only were taken, and culture media varied. They further noted that changing recommendations in this area would amount to starting a screening campaign (albeit in a selected population) but screening is out of scope of CG149, and a single post hoc study is of limited relevance to any debate on group B streptococcus testing. It was finally noted that health economic data would be needed to assess any impact.

Impact statement

The new evidence indicates that women with prelabour rupture of membranes between 34 and 37 weeks 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. CG149 currently 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.

It should be noted that in NICE CG70 Inducing labour, recommendation 1.2.2.2 states: 'If a woman has preterm prelabour rupture of membranes 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).'

Additionally, NICE NG25 Preterm labour and birth makes recommendations on identifying infection in women with preterm prelabour rupture of membranes, but does not discuss testing for group B streptococcus colonisation or using colonisation status to make decisions on timing of delivery.

The impact of the evidence for CG149, CG70 and NG25 may need to be considered, though the post-hoc nature of the evidence should be taken into account. The study authors stated: 'We acknowledge that this was a secondary analysis of 2 randomised trials, not pre-specified as such in the trial protocols, so our findings should be validated before they are applied in clinical practice.' Further limitations noted by the topic experts also need to be considered in assessing the potential impact of the study. The health economics of any impact would also need to be examined.

New evidence identified that may impact on the guideline.

New area outside remit of original guideline: late-onset neonatal infection

A 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). This goes beyond the remit of CG149 which covers early-onset neonatal infection (defined as within 72 hours of birth). The topic overview for the quality standard states: 'This quality standard will cover the use of antibiotics to prevent and treat neonatal infection in newborn babies (both term and preterm) from birth to 28 days in primary (including community) and secondary care.'

The 4-year surveillance review was therefore widened to include evidence for late-onset neonatal infection as defined in the quality statement above.

Several studies in late-onset infection were identified and have been allocated to the following new questions (based on the existing questions for early-onset infection):

NQ – 02 Which maternal and fetal risk factors for late-onset neonatal infection/sepsis should be used to guide management?

This question was not addressed by the guideline.

2-year Evidence Update/Topic expert feedback
No evidence or feedback was identified through these routes as only the 4-year surveillance sift considered late-onset neonatal infection.

Surveillance decision

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

Chorioamnionitis

4-year surveillance summary
A multicentre retrospective analysis[8] examined prospectively collected data on 8,330 very-low-birth-weight infants less than 32 weeks' gestational age to determine the incidence of chorioamnionitis and its effect on sepsis. A total of 1,480 (18%) infants were exposed to chorioamnionitis. After adjusting for confounding factors, infants exposed to chorioamnionitis had a significantly lower risk of late-onset bacterial sepsis (though risk of early-onset sepsis was higher).

Impact statement
Evidence was identified on the association of chorioamnionitis with lower risk of late-onset neonatal sepsis in very-low-birth-weight infants less than 32 weeks' gestation. CG149 does not currently cover late-onset infection.

New evidence identified that may impact on the guideline.

NQ – 03 Which risk factors in the baby (including symptoms and signs) should raise suspicion of late-onset infection/sepsis?

This question was not addressed by the guideline.

2-year Evidence Update/Topic expert feedback
No evidence or feedback was identified through these routes as only the 4-year surveillance sift considered late-onset neonatal infection.

Surveillance decision

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

Exposure to enteral contrast

4-year surveillance summary
A prospective cohort study[41] of infants over 3 days old admitted to a level 4 neonatal intensive care unit for whom a blood culture was drawn for suspected late-onset sepsis investigated risk factors associated with bloodstream infections. Six-hundred and eighty eligible episodes of suspected infection were recorded in 409 infants. In a multivariate analysis, enteral contrast within the preceding 48 hours was the most significant risk factor for laboratory-confirmed infection (odds ratio 9.6) followed by apnea, hypotension and presence of a central venous catheter (odds ratios ranging from 2.5 to 2.9).

Small for gestational age

4-year surveillance summary
A prospective, multicentre study[42] of 5,886 very-low-birth-weight infants from 23 to less than 32 weeks' post menstrual age examined risk of late-onset sepsis in infants born small for gestational age. In small for gestational age infants (n=692), incidence of late-onset sepsis was significantly greater than among infants not small for gestational age. This difference was only observed among infants with a gestational age of 27 to less than 32 weeks and attributed to sepsis episodes with coagulase-negative staphylococci. Different treatment modalities (such as more frequent use of central venous lines) and longer duration of invasive therapies (parenteral nutrition, mechanical ventilation, hospitalisation) may have accounted for the increased sepsis risk with coagulase-negative staphylococci. In a multivariate logistic regression analysis, higher gestational age, treatment with antenatal steroids, German descendance, and prophylaxis with glycopeptide antibiotics were shown to be significantly protective against late-onset sepsis. In contrast, longer duration of parenteral nutrition and being small for gestational age were found to be significant risk factors.

Clinical signs

4-year surveillance summary
A prospective study[43] of 83 episodes of suspected late-onset sepsis in 67 preterm infants investigated the association between clinical signs and late-onset sepsis. Infants were diagnosed as 'clinical late-onset sepsis' (C-reactive protein greater than 10 mg/litre); 'culture-proven late-onset sepsis' (C-reactive protein greater than 10 mg/litre AND positive blood cultures); or 'late-onset sepsis not present'. Clinical late-onset sepsis was diagnosed in 20/83 episodes, 19 cases were found to have culture-proven late-onset sepsis. Clinical signs significantly associated with clinical late-onset sepsis were capillary refill time greater than 2 seconds, and decreased responsiveness, whereas there was a negative association with gastric residuals. The most marked association was found for a greater

central–peripheral temperature difference greater than 2°C. In culture-proven late-onset sepsis an increased heart rate, prolonged capillary refill time, and again an increased central-peripheral temperature difference had a significant association with sepsis, whereas gastric residuals were negatively associated. Regression analysis showed that central-peripheral temperature difference was the most striking clinical sign associated with both clinical- and culture-proven late-onset sepsis.

Various risk factors

4-year surveillance summary

A national surveillance study[44] including 1,695 infants (birth weight less than 1501 grams) from neonatal intensive care units assessed the epidemiology of late-onset bloodstream infections together with risk factors and the distribution of causative pathogens. Four hundred and twenty seven episodes of late-onset infection were diagnosed with a frequency of 25%. In multivariate analysis, late-onset infection was significantly associated with: surgical procedures, lower gestational age, intravascular catheters (increased use/longer duration), duration of total parenteral nutrition, increased length of mechanical ventilation or continuous positive airway pressure, duration of antibiotic use, and occurrence of more than 1 infection. Microorganisms isolated in infants with late-onset infection were dominated by Gram-positive cocci, and predominantly by coagulase-negative staphylococci (63%).

Glucosuria

4-year surveillance summary

A prospective observational cohort study[45] in 316 preterm infants (less than 34 weeks' gestation) examined glucosuria as an early marker of late-onset sepsis. Glucosuria was measured daily and patients were followed for occurrence of late-onset sepsis. Glucosuria was found in 66% of infants, and sepsis was suspected 157 times in 123 infants. Late-onset sepsis was found in 47% of 157 suspected episodes. The presence of glucosuria was significantly associated with late-onset sepsis with sensitivity 69% and specificity 54% (positive likelihood ratio 1.49). After adjustment for gestational age, birth weight, and postnatal age, this association weakened and was no longer significant. An increase in glucosuria 48–24 hours before onset of symptoms was not associated with late-onset sepsis.

Cellular immune status

4-year surveillance summary

A prospective study[46] of 40 preterm infants (gestational week 26–30) and 10 healthy full-term controls (gestational week 37–40) aimed to identify parameters in cellular immune status for predicting late-onset sepsis. Ten-colour flow-cytometric analyses of lymphocyte subpopulations were performed between the 2nd and the 6th day of life, with a follow-up until the preterm infant reached the calculated gestational age of week 40. Ten preterm infants showed events within the first week of life and were excluded from the analysis. Among the other 30 infants, the 12 who developed late-onset sepsis had a significantly elevated proportion of double-negative T cells, and significantly decreased immune-regulatory CD56bright and CD56negCD16+ natural killer cells, compared to infants without sepsis.

Summary

Impact statement

Evidence was identified for the following as potential risk factors for late-onset neonatal infection: exposure to enteral contrast; apnea; hypotension; being small for gestational age; prolonged capillary refill time; elevated central–peripheral temperature difference; surgical procedures; lower gestational age; intravascular catheters (increased use/longer duration); duration of total parenteral nutrition; increased length of mechanical ventilation or

continuous positive airway pressure; duration of antibiotic use; occurrence of more than 1 infection; glucosuria; natural killer cells and double negative-T cell counts. CG149 does not currently cover late-onset infection.

New evidence identified that may impact on the guideline

NQ – 04 **What investigations of asymptomatic babies after birth are useful in identifying those who should/not be treated for late-onset neonatal infection or determining the treatment strategy?**

NQ – 05 **What investigations should be performed prior to commencing treatment in:**
- babies with symptoms
- babies with risk factors without symptoms?

These questions were not addressed by the guideline.

2-year Evidence Update/Topic expert feedback
No evidence or feedback was identified through these routes as only the 4-year surveillance sift considered late-onset neonatal infection.

Surveillance decision

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

Amyloid A

4-year surveillance summary
A systematic review[47] of 77 studies (16 rated as high quality) examined the diagnostic utility of biomarkers for sepsis in neonates with gestational age greater than 24 weeks in their first 28 days of life with suspected sepsis. C-reactive protein (CRP) was the most extensively studied biomarker evaluated, though no data was reported by the review authors for this marker. The high-quality studies indicated that the acute phase protein serum amyloid A had high sensitivity, both at onset of symptoms and 2 days after. The studies evaluating serum amyloid A presented a variable positive predictive value (0.67 and 0.92) but a consistently high negative predictive value (0.97 and 1.00).

Procalcitonin

4-year surveillance summary
A study[48] examined procalcitonin versus C-reactive protein and white blood cell count for therapeutic monitoring of sepsis manifesting after 3 days of life. Procalcitonin was measured in 52 infected and 88 uninfected neonates. Differences between the infected and uninfected groups in procalcitonin and C-reactive protein concentrations were highly significant, but no significant differences were noted for white blood cell count. The cut-off values and diagnostic ability of each test were: procalcitonin (2.06 nanograms/ml; sensitivity 75%, specificity 81%, positive predictive value 62%, negative predictive value 89%); C-reactive protein (5.0 mg/litre; sensitivity 67%, specificity 74%, positive predictive value 42%, negative predictive value 89%), and white blood cell count (11.9 x109/l; sensitivity 51%, specificity 51%, positive predictive value 23%, negative predictive value 78%).

A multicentre prospective cohort study[49] in 2047 febrile infants aged 7 to 91 days admitted for fever to pediatric emergency departments assessed procalcitonin for detecting serious

bacterial infection. Serious bacterial infection was defined as pathogenic bacteria in a positive culture of blood, cerebrospinal fluid, urine, or stool samples, including bacteremia and bacterial meningitis classified as invasive bacterial infections. Among the 2047 infants included, 139 (7%) had a serious bacterial infection and 21 (1%) had an invasive bacterial infection. Procalcitonin had an area under the curve of 0.81, similar to that for C-reactive protein (0.80). The area under the curve for detection of invasive bacterial infection for procalcitonin (0.91) was significantly higher than that for the C-reactive protein (0.77). Using a cutoff value of 0.3 nanograms/ml for procalcitonin and 20 mg/litre for C-reactive protein, negative likelihood ratios were 0.3 for identifying serious bacterial infections and 0.1 and 0.3 for identifying invasive bacterial infection, respectively. Similar results were obtained for the subgroup of infants younger than 1 month and for those with fever lasting less than 6 hours.

Tumour necrosis factor-alpha

4-year surveillance summary

A systematic review and meta-analysis[33] of 23 trials examined tumour necrosis factor-alpha as a diagnostic marker for neonatal sepsis. Tumour necrosis factor-alpha showed moderate accuracy in diagnosing late-onset neonatal sepsis (sensitivity=0.68, specificity=0.89). It was also found that the northern hemisphere group in the test had higher sensitivity (0.84) and specificity (0.83).

Neutrophil CD64

4-year surveillance summary

A study[34] examined the diagnostic accuracy and prognostic value of the neutrophil CD64 expression index in 129 very low birth weight neonates as a marker of early-onset sepsis. The CD64 index was found to an independent risk factor for late-onset infections in that increased expression of the CD64 index was significantly associated with subsequent infections.

A prospective observational cohort study[50] assessed neutrophil CD64 as a diagnostic marker for clinical sepsis (based on a hematologic score) and as an additional marker with hematologic parameters for culture-proven sepsis in neonates. Hematologic and CD64 data were available on 1,156 sepsis evaluations done in 684 infants, of whom 411 (36%) had positive clinical sepsis. The CD64 index had an area under the curve of 0.71. A CD64 cut point of 2.19 for late-onset clinical sepsis was calculated with a sensitivity of 78%, a specificity of 59%, and a negative predictive value of 81%. Neutrophil CD64, in combination with the absolute neutrophil count or the absolute band count, had the highest sensitivity (91%) and specificity (93%), respectively, to diagnose culture-proven sepsis.

A study[51] of 60 infants with neonatal sepsis and 60 infants without sepsis determined whether neutrophil CD64 combined with procalcitonin, C-reactive protein and white blood cell count can increase the sensitivity and accuracy of neonatal sepsis diagnosis. Serum levels of neutrophil CD64, procalcitonin, C-reactive protein and white blood cell count were significantly higher in the sepsis group than non-sepsis group. The sensitivities of neutrophil CD64, procalcitonin, C-reactive protein and white blood cell count at the recommended cut-off level for all infants were 80%, 68%, 39% and 52%, respectively. The best combination was neutrophil CD64 and procalcitonin, which had a sensitivity of 91%, largest area under the curve of 0.922, and a negative predictive value of 89%. However by using an optimal cut-off value, the sensitivities of all 4 biomarkers for the diagnosis of neonatal sepsis were increased to 96%. Except for white blood cell count, the birth weight and gestational age had no effects on the diagnostic value of these serum biomarkers.

Lipopolysaccharide binding protein

4-year surveillance summary

A prospective observational study[52] examined the value of lipopolysaccharide binding protein for diagnosis of late-onset neonatal sepsis in very low birth weight infants. Among 54 infants, there were 26 suspected late-onset sepsis episodes, of which 17 were confirmed. Lipopolysaccharide binding protein levels were significantly higher in confirmed episodes. The area under the curve of lipopolysaccharide binding protein was 0.89. A cut-off of 17.5 micrograms/ml had a sensitivity of 94%, a specificity of 78%, a positive predictive value of 89% and a negative predictive value of 88%.

Presepsin

4-year surveillance summary

A prospective study[53] of newborns less than 32 weeks' gestational age (n=19 with late-onset sepsis, and 21 noninfected controls) at 4 to 60 days' postnatal age examined presepsin for the detection of late-onset sepsis. Presepsin, C-reactive protein and procalcitonin were measured at 0, 1, 3, and 5 days in the late-onset sepsis group, whereas presepsin alone was measured in the control group. Presepsin at enrolment was significantly higher in the late-onset sepsis than the control group and remained higher throughout the study period. In the late-onset sepsis group, presepsin had a borderline reduction at day 1 versus values at enrolment, whereas C-reactive protein and procalcitonin at day 1 did not differ from baseline values. The area under the curve of presepsin at enrolment was 0.972. The best calculated cutoff was 885 nanograms/l, with 94% sensitivity and 100% specificity. Negative likelihood ratio was 0.05, and positive likelihood ratio was infinity.

Urinary neutrophil gelatinase-associated lipocalin

4-year surveillance summary

A prospective observational study[54] of 136 neonates who underwent more than 1 sepsis evaluation at over 72 hours of age examined urinary neutrophil gelatinase-associated lipocalin as a potential biomarker for late-onset sepsis. Using generalised estimating equations controlling for gender, gestational and postnatal age, acute kidney injury, and within-patient correlations, the predicted mean log urinary neutrophil gelatinase-associated lipocalin values of culture-positive sepsis and presumed sepsis versus negative sepsis evaluations differed significantly. At a cutoff of greater than 50 nanograms/ml, urinary neutrophil gelatinase-associated lipocalin discriminated between culture-positive sepsis and culture-negative sepsis evaluations with sensitivity 86%, specificity 56%, positive predictive value 41%, and negative predictive value 92%.

Soluble receptor for advanced glycation end products

4-year surveillance summary

A prospective study[55] assessed the plasma levels of soluble receptor for advanced glycation end products in infected and non-infected preterm neonates and compared their diagnostic values with standard infection biomarkers. The 33 neonates included were divided into 3 subgroups: infected, septic, or non-infected controls. Significantly lower values of soluble receptor for advanced glycation end products were seen in the septic subgroup. A numerically but not significantly higher value was seen in the infected subgroup compared to controls. Interobserver concordance showed 70% agreement in measured values detected in infection and sepsis. Procalcitonin was used as the gold standard.

Summary

Impact statement
Evidence was identified for the following as potential biomarkers for diagnosing late-onset neonatal infection: serum amyloid A; procalcitonin; tumour necrosis factor-alpha; neutrophil CD64; lipopolysaccharide binding protein; presepsin; urinary neutrophil gelatinase-associated lipocalin; and soluble receptor for advanced glycation end products. CG149 does not currently cover late-onset infection.

New evidence identified that may impact on the guideline

NQ – 06 What is the optimal antibiotic treatment regimen for suspected late-onset neonatal infection?

This question was not addressed by the guideline.

2-year Evidence Update/Topic expert feedback
No evidence or feedback was identified through these routes as only the 4-year surveillance sift considered late-onset neonatal infection.

Surveillance decision

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

Vancomycin

4-year surveillance summary
A study[56] of 4364 infants discharged from 348 neonatal intensive care units examined empirical vancomycin therapy for coagulase-negative staphylococcus bloodstream infections. Empirical vancomycin therapy was defined as vancomycin exposure on the day of the first positive blood culture. Delayed therapy was defined as vancomycin exposure 1–3 days after the first positive blood culture. Analyses controlled for gestational age, small-for-gestational age status, postnatal age on the day of the first positive culture, oxygen requirement, ventilator support and inotropic support on the day the first positive culture was obtained. A total of 2848 (65%) infants were treated with empirical vancomycin. The median postnatal age at first positive culture was 14 days. In unadjusted and multivariable analyses, no significant difference in 30-day mortality was seen for infants treated with empirical or delayed vancomycin therapy. The median duration of bacteremia was significantly longer by 1 day for infants with delayed vancomycin therapy.

Impact statement
The median duration of bacteremia was 1 day longer in infants with coagulase-negative staphylococcus bloodstream infections who received delayed vancomycin therapy. Despite this, empirical vancomycin therapy for coagulase-negative staphylococcus bloodstream infections was not associated with improved mortality. CG149 does not currently cover late-onset infection.

New evidence identified that may impact on the guideline.

Research recommendations

Prioritised research recommendations

At 4-year and 8-year surveillance reviews of guidelines published after 2011, we assess progress made against prioritised research recommendations. We may then propose to remove research recommendations from the NICE version of the guideline and the NICE database for research recommendations. The research recommendations will remain in the full versions of the guideline. See NICE's research recommendations process and methods guide 2015 for more information.

These research recommendations were deemed priority areas for research by the Guideline Committee; therefore, at this 4-year surveillance review time point a decision **will** be taken on whether to retain the research recommendations or stand them down.

We applied the following approach:

- New evidence relevant to the research recommendation was found and an update of the related review question is planned.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database. If needed, a new research recommendation may be made as part of the update process.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.
  - The research recommendation will be retained because there is evidence of research activity in this area.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because evidence supports current recommendations.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database because further research is unlikely to impact on the guideline.
- Ongoing research relevant to the research recommendation was found.
  - The research recommendation will be retained and evidence from the ongoing research will be considered when results are published.
- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
  - The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.
- The research recommendation would be answered by a study design that was not included in the search (usually systematic reviews or randomised controlled trials).
  - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.
- The new research recommendation was made during a recent update of the guideline.
  - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

RR – 01 What is the clinical and cost effectiveness of intrapartum antibiotic prophylaxis targeting group B streptococcus and guided by routine antenatal screening?

New evidence related to the clinical effectiveness of intrapartum antibiotic prophylaxis targeting group B streptococcus and guided by routine antenatal screening was found but an

update is not planned because the limited quality of the evidence is unlikely to affect the guideline. Additionally, a review of the UK National Screening Committee recommendation on Group B Streptococcus screening in pregnancy is due to publish in 2017.

Surveillance decision

This research recommendation should be retained in the NICE version of the guideline and the NICE research recommendations database.

RR – 02 Which risk factors for early-onset neonatal infection, clinical symptoms and signs of infection, and laboratory investigations should be used to identify babies who should receive antibiotics?

New evidence related to maternal risk factors was found and an update is planned.

Surveillance decision

It was proposed to remove the research recommendation from the NICE version of the guideline and the NICE research recommendations database because an update is planned. However topic experts felt the evidence found did not relate to the majority of the research recommendation. Therefore it was decided to retain this research recommendation based on the feedback on its importance.

RR – 03 What is the clinical and cost effectiveness of intrapartum antibiotic prophylaxis using benzylpenicillin in women with preterm labour?

No new information was identified at any surveillance review.

Surveillance decision

It was proposed to remove the research recommendation from the NICE version of the guideline and the NICE research recommendations database because no evidence was found. However topic experts felt the research recommendation remained relevant. Therefore it was decided to retain this research recommendation based on the feedback on its importance.

RR – 04 What is the clinical and cost effectiveness of laboratory investigations used individually or in combination to exclude early-onset neonatal infection in babies receiving antibiotics for suspected infection?

New evidence related to laboratory investigations was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.

Surveillance decision

This research recommendation should be retained because there is evidence of research activity in this area.

RR – 05 What is the optimal duration of treatment (course length) in babies who receive antibiotics for confirmed early-onset neonatal infection?

No new information was identified at any surveillance review.

Surveillance decision

It was proposed to remove the research recommendation from the NICE version of the guideline and the NICE research recommendations database because no evidence was

found. However topic experts felt the research recommendation remained relevant. Therefore it was decided to retain this research recommendation based on the feedback on its importance.

Other research recommendations

The following research recommendations were not deemed priority areas for research by the guideline committee. No decisions will be taken on the status of these research recommendations or stand them down.

RR – 06 How does each step in the care pathway for prevention and treatment of early-onset neonatal infection impact on babies and their families?

New evidence was found on parental consent in neonatal antibiotic use but an update is not planned because the evidence supports the current guideline recommendations.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 07 What is the clinical and cost effectiveness of information and support offered to parents and carers of babies who have received antibiotics for suspected or proven early-onset neonatal infection?

New evidence was found on parental consent in neonatal antibiotic use but an update is not planned because the evidence supports the current guideline recommendations.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 08 What is the optimal dosage regimen for benzylpenicillin when used as intrapartum antibiotic prophylaxis to prevent early-onset neonatal infection?

No new information was identified at any surveillance review.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 09 What is the incidence in England and Wales of resistance to commonly used antibiotics among bacteria that cause early-onset neonatal infection?

No new information was identified at any surveillance review.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 10 What is the optimal antibiotic treatment regimen for early-onset neonatal meningitis?

No new information was identified at any surveillance review.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 11 What is the optimal antibiotic dosage regimen for the treatment of early-onset neonatal infection?

No new information was identified at any surveillance review.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 12 What is the incidence and severity of adverse effects with antibiotics used to prevent or treat early-onset neonatal infection?

No new information was identified at any surveillance review.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 13 What are the core exposures and outcomes that should be used to evaluate clinical effectiveness of antibiotics to prevent or treat early-onset neonatal infection?

No new information was identified at any surveillance review.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 14 What is the clinical and cost effectiveness of different models of care for the prevention and treatment of early-onset neonatal infection?

No new information was identified at any surveillance review.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

References

1. Wickham S. (2014) Who safeguards mothers? Practising Midwife 17:26.

2. Rastogi S, Rojas M, Rastogi D et al. (2015) Neonatal morbidities among full-term infants born to obese mothers. Journal of Maternal-Fetal & Neonatal Medicine 28:829-835.

3. Chan GJ, Lee AC, Baqui AH et al. (2015) Prevalence of early-onset neonatal infection among newborns of mothers with bacterial infection or colonization: a systematic review and meta-analysis. BMC Infectious Diseases 15:118.

4. Hanke K, Hartz A, Manz M et al. (2015) Preterm prelabor rupture of membranes and outcome of very-low-birth-weight infants in the German Neonatal Network. PLoS ONE [Electronic Resource] 10:e0122564.

5. Agakidis C, Agakidou E, Philip TS et al. (2011) Labor epidural analgesia is independent risk factor for neonatal pyrexia. J Matern.Fetal Neonatal Med. 24:1128-1132.

6. Wassen MM, Winkens B, Dorssers EM et al. (2014) Neonatal sepsis is mediated by maternal fever in labour epidural analgesia. Journal of Obstetrics & Gynaecology 34:679-683.

7. Arayici S, Kadioglu SG, Oncel MY et al. (2014) The effect of histological chorioamnionitis on the short-term outcome of preterm infants <32 weeks: a single-center study. Journal of Maternal-Fetal & Neonatal Medicine 27:1129-1133.

8. Garcia-Munoz RF, Galan HG, Figueras AJ et al. (2014) Outcomes of very-low-birth-weight infants exposed to maternal clinical chorioamnionitis: a multicentre study. Neonatology 106:229-234.

9. Garcia-Munoz RF, Galan Henriquez GM, and Ospina CG. (2014) Morbidity and mortality among very-low-birth-weight infants born to mothers with clinical chorioamnionitis. Pediatrics & Neonatology 55:381-386.

10. Kacerovsky M, Musilova I, Andrys C et al. (2014) Prelabor rupture of membranes between 34 and 37 weeks: the intraamniotic inflammatory response and neonatal outcomes. American Journal of Obstetrics & Gynecology 210:325.

11. Stimac M, Juretic E, Vukelic V et al. (2014) Effect of chorioamnionitis on mortality, early onset neonatal sepsis and bronchopulmonary dysplasia in preterm neonates with birth weight of < 1,500 grams. Collegium Antropologicum 38:167-171.

12. Wortham JM, Hansen N, I, Schrag SJ et al. (2016) Chorioamnionitis and Culture-Confirmed, Early-Onset Neonatal Infections. Pediatrics 137:1-11.

13. Brigtsen AK, Jacobsen AF, Dedi L et al. (2015) Maternal Colonization with Group B Streptococcus Is Associated with an Increased Rate of Infants Transferred to the Neonatal Intensive Care Unit. Neonatology 108:157-163.

14. Kalin A, Acosta C, Kurinczuk JJ et al. (2015) Severe sepsis in women with group B Streptococcus in pregnancy: an exploratory UK national case-control study. BMJ Open 5:e007976.

15. van dH, D P, van KS et al. (2014) Can neonatal sepsis be predicted in late preterm premature rupture of membranes? Development of a prediction model. European Journal of Obstetrics, Gynecology, & Reproductive Biology 176:90-95.

16. Baker CJ, Carey VJ, Rench MA et al. (2014) Maternal antibody at delivery protects neonates from early onset group B streptococcal disease. Journal of Infectious Diseases 209:781-788.

17. Musilova I, Kacerovsky M, Andrys C et al. (2014) The fetal splenic vein flow pattern and fetal inflammatory response in the preterm prelabor rupture of membranes. Journal of Maternal-Fetal & Neonatal Medicine 27:770-774.

18. Escobar GJ, Puopolo KM, Wi S et al. (2014) Stratification of risk of early-onset sepsis in newborns > 34 weeks' gestation. Pediatrics 133:30-36.

19. Ohlsson A and Shah VS. (2014) Intrapartum antibiotics for known maternal Group B streptococcal colonization. SO: Cochrane Database of Systematic Reviews .

20. Hakansson S, Kallen K, Bullarbo M et al. (2014) Real-time PCR-assay in the delivery suite for determination of group B streptococcal colonization in a setting with risk-based antibiotic prophylaxis. Journal of Maternal-Fetal & Neonatal Medicine 27:328-332.

21. Daher RK, Stewart G, Boissinot M et al. (2014) Isothermal recombinase polymerase amplification assay applied to the detection of group B streptococci in vaginal/anal samples. Clinical Chemistry 60:660-666.

22. Kurz E and Davis D. (2015) Routine culture-based screening versus risk-based management for the prevention of early-onset group B streptococcus disease in the neonate: a systematic review. JBI Database Of Systematic Reviews And Implementation Reports 13:206-246.

23. Siriwachirachai T, Sangkomkamhang US, Lumbiganon P et al. (2014) Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections. SO: Cochrane Database of Systematic Reviews .

24. Heath PT and Jardine LA. (2014) Neonatal infections: group B streptococcus. Clinical Evidence 2014,2014.

25. Hornik CP, Benjamin DK, Becker KC et al. (2012) Use of the complete blood cell count in early-onset neonatal sepsis. Pediatr.Infect.Dis.J 31:799-802.

26. Duvoisin G, Fischer C, Maucort-Boulch D et al. (2014) Reduction in the use of diagnostic tests in infants with risk factors for early-onset neonatal sepsis does not delay antibiotic treatment. Swiss Medical Weekly 144:w13981.

27. Vouloumanou EK, Plessa E, Karageorgopoulos DE et al. (2011) Serum procalcitonin as a diagnostic marker for neonatal sepsis: a systematic review and meta-analysis. Intensive Care Med. 37:747-762.

28. Jost C, Bercot B, Jacquier H et al. (2014) Xpert GBS assay for rapid detection of group B streptococcus in gastric fluid samples from newborns. Journal of Clinical Microbiology 52:657-659.

29. Decembrino L, De AM, Pozzi M et al. (2015) Serum Calprotectin: A Potential Biomarker for Neonatal Sepsis. Journal of Immunological Research 2015:147973.

30. Hou T, Huang D, Zeng R et al. (2015) Accuracy of serum interleukin (IL)-6 in sepsis diagnosis: a systematic review and meta-analysis. International journal of clinical and experimental medicine 8:15238-15245.

31. Zhou M, Cheng S, Yu J et al. (2015) Interleukin-8 for diagnosis of neonatal sepsis: a meta-analysis. PLoS ONE [Electronic Resource] 10:e0127170.

32. Luo J, Xu F, Lu GJ et al. (2014) Low mannose-binding lectin (MBL) levels and MBL genetic polymorphisms associated with the risk of neonatal sepsis: An updated meta-analysis. [Review]. Early Human Development 90:557-564.

33. Lv B, Huang J, Yuan H et al. (2014) Tumor necrosis factor-alpha as a diagnostic marker for neonatal sepsis: a meta-analysis. Thescientificworldjournal 2014:471463.

34. Motta M, Zini A, Regazzoli A et al. (2014) Diagnostic accuracy and prognostic value of the CD64 index in very low birth weight neonates as a marker of early-onset sepsis. Scandinavian Journal of Infectious Diseases 46:433-439.

35. Mussap M, Puxeddu E, Puddu M et al. (2015) Soluble CD14 subtype (sCD14-ST) presepsin in premature and full term critically ill newborns with sepsis and SIRS. Clinica Chimica Acta 451:A-70.

36. Alshaikh B, Dersch-Mills D, Taylor R et al. (2012) Extended interval dosing of gentamicin in premature neonates </= 28-week gestation. Acta Paediatr. 101:1134-1139.

37. Coggins SA, Wynn JL, Hill ML et al. (2013) Use of a computerized C-reactive protein (CRP) based sepsis evaluation in very low birth weight (VLBW) infants: a five-year experience. PLoS One 8:e78602.

38. Lacaze-Masmonteil T, Rosychuk RJ, and Robinson JL. (2014) Value of a single C-reactive protein measurement at 18 h of age. Archives of Disease in Childhood Fetal & Neonatal Edition 99:F76-F79.

39. Mukherjee A, Davidson L, Anguvaa L et al. (2015) NICE neonatal early onset sepsis guidance: greater consistency, but more investigations, and greater length of stay. Archives of Disease in Childhood Fetal & Neonatal Edition 100:F248-F249.

40. Tajik P, van dH, D P et al. (2014) Using vaginal Group B Streptococcus colonisation in women with preterm premature rupture of membranes to guide the decision for immediate delivery: a secondary analysis of the PPROMEXIL trials. BJOG: An International Journal of Obstetrics & Gynaecology 121:1263-1272.

41. Padula MA, Dewan ML, Shah SS et al. (2014) Risk factors associated with laboratory-confirmed bloodstream infections in a tertiary neonatal intensive care unit. Pediatric Infectious Disease Journal 33:1027-1032.

42. Troger B, Gopel W, Faust K et al. (2014) Risk for late-onset blood-culture proven sepsis in very-low-birth weight infants born small for gestational age: a large multicenter study from the German Neonatal Network. Pediatric Infectious Disease Journal 33:238-243.

43. Ussat M, Vogtmann C, Gebauer C et al. (2015) The role of elevated central-peripheral temperature difference in early detection of late-onset sepsis in preterm infants. Early Human Development.91 (12) (pp 677-681), 2015.Date of Publication: 2015. 677-681.

44. Wojkowska-Mach J, Gulczynska E, Nowiczewski M et al. (2014) Late-onset bloodstream infections of Very-Low-Birth-Weight infants: data from the Polish Neonatology Surveillance Network in 2009-2011. BMC Infectious Diseases 14:339.

45. Bekhof J, Kollen BJ, Kok JH et al. (2015) Glucosuria as an early marker of late-onset sepsis in preterms: a prospective cohort study. BMC Pediatrics 15:125.

46. Bochennek K, Fryns E, Wittekindt B et al. (2016) Immune cell subsets at birth may help to predict risk of late-onset sepsis and necrotizing enterocolitis in preterm infants. Early Human Development 93:9-16.

47. Hedegaard SS, Wisborg K, and Hvas AM. (2015) Diagnostic utility of biomarkers for neonatal sepsis--a systematic review. [Review]. Infectious Diseases 47:117-124.

48. Kordek A, Loniewska B, Podraza W et al. (2014) Usefulness of estimation of blood procalcitonin concentration versus C-reactive protein concentration and white blood cell count for therapeutic monitoring of sepsis in neonates. [Review]. Postepy Higieny i Medycyny do Swiadczalnej (Online) 68:1516-1523.

49. Milcent K, Faesch S, Guen CGL et al. (2016) Use of Procalcitonin Assays to Predict Serious Bacterial Infection in Young Febrile Infants. JAMA Pediatrics.170 (1) (pp 62-69), 2016.Date of Publication: January 2016. 62-69.

50. Streimish I, Bizzarro M, Northrup V et al. (2014) Neutrophil CD64 with hematologic criteria for diagnosis of neonatal sepsis. American Journal of Perinatology 31:21-30.

51. Yang AP, Liu J, Yue LH et al. (2016) Neutrophil CD64 combined with PCT, CRP and WBC improves the sensitivity for the early diagnosis of neonatal sepsis. Clinical Chemistry & Laboratory Medicine 54:345-351.

52. Leante-Castellanos JL, de Guadiana-Romualdo LG, Fuentes-Gutierrez C et al. (2015) The value of lipopolysaccharide binding protein for diagnosis of late-onset neonatal sepsis in very low birth weight infants. Journal of Perinatal Medicine 43:253-257.

53. Poggi C, Bianconi T, Gozzini E et al. (2015) Presepsin for the detection of late-onset sepsis in preterm newborns. Pediatrics 135:68-75.

54. Pynn JM, Parravicini E, Saiman L et al. (2015) Urinary neutrophil gelatinase-associated lipocalin: potential biomarker for late-onset sepsis. Pediatric Research 78:76-81.

55. Zolakova B, Zolak V, Hatok J et al. (2016) Soluble receptor for advanced glycation end products in late-onset neonatal infection. Bratislavske Lekarske Listy 117:15-18.

56. Ericson JE, Thaden J, Cross HR et al. (2015) No survival benefit with empirical vancomycin therapy for coagulase-negative staphylococcal bloodstream infections in infants. Pediatric Infectious Disease Journal 34:371-375.