# Neonatal early onset sepsis: a reflection on the NICE guidance

Neonatal early onset sepsis is a significant clinical problem requiring prompt identification and treatment of affected infants. Although the National Institute of Health and Care Excellence (NICE) guidance is helpful in defining a consistent approach to this topic, there remain large numbers of asymptomatic infants (with risk factors) who receive investigations and longer courses of antibiotics because of raised C-reactive protein. There is an urgent need to re-evaluate this and develop more specific investigations to confirm sepsis in order to prevent unaffected infants receiving unnecessary antibiotics.

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## Key points

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1. NICE guidance defines a consistent approach to management of early onset sepsis based on risk factors, clinical parameters and C-reactive protein (CRP) levels.
2. Raised CRP levels in asymptomatic infants are not a good predictor of sepsis in isolation and can lead to investigations and prolonged courses of antibiotics.
3. Further research is required into CRP levels in asymptomatic patients and alternative more sensitive investigations.

NICE is the UK health organisation responsible for providing national guidance to promote uniformity in quality and practice based on best available evidence. The NICE guideline CG149 was published in August 2012 to provide recommendations for the management of infants with risk factors for early onset sepsis (EOS).[1] The guidance outlined a strategy for determining which infants had septic screens based on risk factors, and used biochemical and clinical parameters to guide management. The guidance emphasises parental choice and rightly prompts the early identification and treatment of 'at risk' infants.

Early onset bacterial infection in neonates, defined within 72 hours of birth, carries high mortality and morbidity. The rate of EOS is approximately 1-1.5 per 1,000 births.[2] Before this guidance was published, there was a wide variation in management protocols and definition of 'risk factors' within different neonatal units.

Although the identification and treatment of symptomatic babies is essential, defining the management of asymptomatic infants with risk factors alone is a challenge, particularly in the context of the large number of infants in this group and the lack of good tests to confirm or definitively rule out sepsis. It is known that neonatal blood cultures have poor yield,[3] and the interpretation and actions based on non-specific inflammatory markers eg C-reactive protein (CRP) in well infants has not been well studied.

Publication of the NICE guideline CG149, *Neonatal Infection: Antibiotics for Prevention and Treatment*,[1] aimed to unify the medical care of all newborns with suspected EOS. The stated aims were:

1. prioritising the treatment of sick babies
2. minimising the impact of management pathways on healthy women and babies
3. observing wise use of antibiotics to avoid the development of resistant organisms.

Unfortunately a number of units have now reported that this guidance has not met its aim of minimising antibiotic exposure in infants who do not have EOS and has led to further investigations, increased lumbar punctures and longer durations of treatment and stay[4,5] for 'at risk' asymptomatic infants with raised inflammatory markers. Although the guidance rightly puts emphasis on the clinical suspicion of sepsis, in practice it is hard to ignore significantly raised CRP in infants who have always been well; this has led to large numbers of healthy infants having a full course of antibiotics and a lumbar puncture on day two. There is evidence that some units have re-defined CRP thresholds to levels greater than 10mg/L (the recommended level given in the guidance) in order to avoid lumbar puncture.[6]

This article evaluates the NICE guidance and comments on some of the evidence underpinning it.

## Who to treat?

To aid in the universal identification of neonates at risk of infection, the CG149 guidelines include two tables. The first is a list of risk factors that relate to events leading up to delivery; the second is a list of clinical risk factors that describe the condition of the baby after delivery.

These are further subdivided into red flags (**TABLE 1**) or non-red flags (**TABLE 2**). If a baby has one red flag or two non-red flag risk factors, the guidance recommends the clinician to start antibiotics once the correct samples have been taken and in a timely fashion (within one hour of the decision to treat). However, if the baby only has one non-red flag risk factor such as premature delivery without prolonged rupture of membranes, that baby can be observed and antibiotics only commenced if the clinical condition warrants it.

In the authors' institution, these guidelines have led to approximately 8% of all newborn babies having a septic screen, equating to about 80 infants treated for each confirmed episode of EOS. Although the risk factor tables in CG149 are easy to use, and the 'red flags' clearly indicated, there are marked differences in practice and interpretation between units that may lead to differing numbers of asymptomatic infants being screened. For example, there may be differences in screening policies for group B streptococcus leading to variation in the proportion of colonised women identified, different thresholds for defining clinical chorioamnionitis and treatment of mothers with antibiotics, differing approaches to ventilation in preterm infants, or glucose and lactate monitoring in asymptomatic infants. In addition it is important that local protocols clearly highlight the difference between the risk factors of prolonged rupture of membranes (≥18 hours before delivery) in preterm infants and pre-labour rupture of membranes in term infants. Rupture of membranes lasting more than 18 hours is very common in primiparous women in labour.

## Investigations before starting antibiotics in the infant

The guidance emphasises the need to perform a blood culture and consider performing a lumbar puncture to obtain a cerebrospinal fluid (CSF) sample if "there is a strong clinical suspicion of infection" before administering the first dose of antibiotics, with the caveat that lumbar puncture could be deferred if it would delay antibiotic dosing. This is uncontroversial and would indicate that asymptomatic infants with risk factors alone should not have a lumbar puncture at this stage. CG149 also suggests performing a CRP at presentation when starting antibiotic treatment in infants with risk factors for infection or clinical indicators of possible infection. The data underpinning the use of CRP in evaluating sepsis are discussed in a following section.

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| Parenteral antibiotic treatment given to the mother 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) |
| Suspected or confirmed infection in another baby in the case of a multiple pregnancy |
| Respiratory distress starting more than four hours after birth |
| Seizures |
| Need for mechanical ventilation in a term baby |
| Signs of shock |

**TABLE 1** 'Red flags' – risk factors to guide antibiotic use. If a baby has one red flag risk factor, the NICE guideline recommends starting antibiotics.

## When to stop treatment?

Once antibiotics have been started, it is important to identify babies who do not have an infection within a reasonable timeframe, to allow treatment to be discontinued. It is also important to identify the small number of babies who do have early onset bacterial infection, in order to perform a lumbar puncture and to make decisions regarding length of treatment.

In order to aid this process of discriminating between the two groups, NICE guidelines recommend a second CRP performed 18-24 hours after presentation. If the CRP is low, the trend in CRP is 'reassuring' (undefined in the NICE guidance) and if the blood cultures are negative at 36 hours, antibiotics can be discontinued, with the proviso that the baby is clinically well and initial suspicion of sepsis was low. The reduction of typical antibiotic course from 48 to 36 hours is very welcome, although some units have been challenged by microbiology departments that cannot report cultures at that time.

## When to continue treatment?

Babies that have been clinically unwell, or those well infants with risk factors and raised CRP, are given a longer course of antibiotics; the duration and type will depend on whether meningitis is present. A lumbar puncture is suggested if the CRP is above 10mg/L, the blood culture is positive or the baby has failed to respond clinically to current antibiotic treatment. The authors' experience is that, although neonatal meningitis is fortunately very rare indeed (~3 per 10,000 births), many well infants have a CRP >10mg/L at 18-24 hours. This has led to more lumbar punctures and several units increasing the threshold of CRP locally to avoid this investigation in well babies.[6] CRP is a very non-specific marker and can be raised in non-infectious conditions; there is a lack of data in healthy infants with risk factors.

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| Invasive group B streptococcal infection in a previous baby |
| Altered behaviour or responsiveness |
| Altered muscle tone (eg floppiness) |
| Feeding difficulties (eg feed refusal) |
| Feed intolerance, including vomiting, excessive gastric aspirates and abdominal distension |
| Abnormal heart rate (bradycardia or tachycardia) |
| Signs of respiratory distress |
| Hypoxia (eg central cyanosis or reduced oxygen saturation level) |
| Jaundice within 24 hours of birth |
| Apnoea |
| Signs of neonatal encephalopathy |
| Need for cardiopulmonary resuscitation |
| Need for mechanical ventilation in a preterm baby |
| Persistent fetal circulation (persistent pulmonary hypertension) |
| Temperature abnormality (<36°C or >38°C) unexplained by environmental factors |
| Unexplained excessive bleeding, thrombocytopenia, or abnormal coagulation (international normalised ratio >2.0) |
| Oliguria persisting beyond 24 hours after birth |
| Altered glucose homeostasis (hypoglycaemia or hyperglycaemia) |
| Metabolic acidosis (base deficit of ≥10mmol/L) |
| Local signs of infection (eg affecting the skin or eye) |

**TABLE 2** 'Non-red flags'. If a baby has two non-red flag risk factors, the NICE guideline recommends starting antibiotics.

## Challenges with interpretation of CRP

CRP is currently the most well studied serum acute phase reactant in the newborn population. The test is readily available, cheap and can give rapid results to clinical teams – as such it is the most commonly used infection marker in neonatal units. Near-patient CRP measurement is also now available. In the context of EOS, the sensitivity of an investigation is more important than its specificity, as the implications of not treating an infected infant are potentially far greater than unnecessarily treating uninfected infants. CRP crosses the placenta in very low levels[7] and therefore maternal and infant CRP should not be linked. CRP starts to rise five to six hours after an initial inflammatory trigger and then peaks at 36-50 hours, with levels falling rapidly as inflammation resolves,[8] with a half-life of 19 hours.[9] This suggests an initial CRP at presentation may be unhelpful in our assessment and management plans, however it does make sense to take samples when inserting a cannula and initiating antibiotics to minimise blood sampling from the infant.

There is very limited evidence around normal CRP levels in healthy newborn infants; in 1985 Shine et al aimed to gain information on normal values of CRP and the diagnostic value in EOS. In that study, 48 cord blood samples were taken and the median CRP value was 0.2mg/L (0.015-6mg/L).[10] There were several infants with confirmed sepsis who had a later rise in their CRP levels. It has also been argued that other neonatal events besides infection (such as meconium aspiration, fetal distress, maternal fever and premature rupture of membranes) can cause a CRP rise, although the current evidence is inconclusive.[11]

The NICE guidance on investigations of the neonate with suspected EOS is based on a range of studies comparing CRP, interleukin-8, interleukin-6, procalcitonin, CSF and blood culture results.[12] One such study looks at the benefits of serial CRP levels; a prospective cohort from 1993-1996 including 1,002 infants of over 36 weeks' gestation across three neonatal intensive care units in California, USA, being treated for presumed EOS. Sensitivity of CRP from initial presentation and at 8-24 hours increased from 39.4% to 92.9%, specificity dropped from 92.5% to 83.9% and positive predictive value increased from 6.7% to 35.4%.[13] There are no large studies available to the NICE guidance authors that focus on the asymptomatic infant. In conclusion, initial CRP at presentation is not helpful in diagnosing or excluding EOS, however, serial CRPs 24 hours apart, if both are under 10mg/mL, are useful in excluding EOS.

More recently, in 2013, Lacaze-Masmonteil et al assessed the value of a single CRP level at 18 hours of age.[14] They found both low sensitivity (64%) and specificity (56%) values but, as might be expected, a high negative predictive value (93%). They concluded that a raised 18-hour CRP in isolation is not a justification to continue antibiotics.

All studies used CRP alongside other criteria, such as clinical condition, blood culture results and acute phase reactants. CRP was not used as a single criterion for discontinuing antibiotics in these studies.[11] The most commonly studied CRP cut-off is 10mg/L, but in view of the physiology of CRP in the first few days of life, how appropriate is this and should we not consider a dynamic reference range? The NICE guidance may be attempting to acknowledge the dynamic ranges in CRP by including evaluation of 'trends' of CRP in individual patients. However, without definition or data underpinning the use of trends in asymptomatic infants, this may lead to further inconsistencies in interpretation and patient management.

## Conclusions

The NICE guideline for EOS comes with the benefits of standardised care, however we must appreciate the evidence for investigation with CRP levels is based on symptomatic infants and there is a lack of robust published evidence for CRP levels, or trends, in asymptomatic infants. In future iterations of the guidance, it may be helpful to put more emphasis on asymptomatic infants and acknowledge that, although low CRP is helpful in ruling out sepsis, it is likely to be unhelpful in predicting sepsis and meningitis (and therefore the need for further investigation with lumbar puncture) in infants who have always been asymptomatic in their first two days of life.

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