What's new in the management of neonatal early-onset sepsis?

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ABSTRACT

The expert guidelines highlighted in this review provide an evidence-based framework for approaching at-risk infants and allow for a more limited and standardised approach to antibiotic use. While these guidelines have significantly reduced antibiotic utilisation worldwide, optimally each unit would individualise their approach to early onset sepsis (EOS) based on the neonatal population they serve and available resources. As advancements in EOS research continue and limitations with sepsis prediction tools are addressed, it is inevitable that our risk stratification and management guidelines will become more precise.

INTRODUCTION

The management and diagnosis of early onset sepsis (EOS) in term and preterm infants continues to evolve with wide variation in practice globally. With the declining incidence of EOS, and a growing emphasis on reducing neonatal exposure to prolonged and unnecessary antimicrobials, many national organisations have updated their diagnostic and treatment guidelines. Given the broad nature of the topic, this review will principally address management considerations in late preterm and term infants.

Risk factors for EOS

The risk of EOS is inversely related to gestational age with the highest rates occurring among infants born between 22 weeks and 28 weeks of gestation (18.47/1000 live births) and lowest in those born at term (0.5/1000 live births).[1 2] Other factors associated with an increased risk for EOS reflect the underlying pathogenesis which involves the ascension of microbes colonising the maternal genitourinary tract into the intrauterine space before or during labour. Maternal colonisation with GBS (group B streptoccus), increasing duration of membrane rupture and intra-amniotic infection (ie, chorioamnionitis) are all associated with increased risk of EOS.[3] Moreover, intra-amniotic infection may trigger preterm labour and premature rupture of membranes—both of which are associated with EOS.[1 4] The development of mathematical models, such as the Neonatal Sepsis Calculator, allows for the relationship between individual neonatal/maternal risk factors and the outcome of EOS in infants ≥34 weeks' gestation to be quantified.[3] However, in infants born <34 weeks' gestation, the independent contribution of any specific factor, other than gestational age, to the risk of EOS is difficult to determine.[5]

The diagnosis of intra-amniotic infection is challenging and can only be definitively established by amniotic fluid culture, Gram stain or biochemical analysis.[6] In the vast majority of women, a diagnosis of 'chorioamnionitis' is made using clinical criteria alone. These criteria lack specificity, are inconsistently applied, and do not distinguish between inflammation and active infection. Consequently, 1%–10% of pregnancies and deliveries are complicated by a diagnosis of 'clinical chorioamnionitis.'[7] This means, that if the clinical diagnosis of chorioamnionitis is considered an absolute indication for empirical antibiotic administration, many healthy infants are ultimately treated with empirical antibiotics to treat suspected sepsis and prevent progression to severe clinical illness.[8 9]

In 2015, the National Institute of Child Health and Human Development assembled a workshop to provide evidence-based guidelines for the diagnosis and management of chorioamnionitis.[10] This expert panel recommended separating this entity into three categories: (1) Isolated maternal fever, (2) Suspected intra-amniotic infection and (3) Confirmed intra-amniotic infection. The panel also recommended replacing the term 'chorioamnionitis' with 'intrauterine inflammation, infection (triple I)'. This verbiage was proposed to reflect a more precise description of this clinical entity and the underlying pathophysiology. In its most recent committee opinion, the American College of Obstetrics and Gynaecology recognised the entity 'isolated maternal fever' (defined as any temperature between 38°C and 38.9°C with no other clinical criteria indicating intra-amniotic infection) as a diagnosis distinct from suspected intra-amniotic infection.[6] Similarly, the current National Institute for Health and Care Excellence (NICE) guidelines separate isolated intrapartum fever and chorioamnionitis as distinct risk factors.[11]

Diagnostic approach to EOS

Recent guidelines from the American Academy of Pediatrics (AAP) and NICE provide updated recommendations on the approach to at-risk infants, particularly for those who are well appearing at birth.[11 12] It is important to note that the guidelines from AAP are divided into infants ≥35 weeks' gestation and ≤34$^{6/7}$ weeks' gestation, while the NICE guidelines address all gestational ages simultaneously, but identify preterm birth before 37 weeks' gestation as a 'red flag'. Previous sepsis guidelines recommended obtaining a blood culture with adjunct laboratory studies and initiating antibiotic therapy based on perinatal risk factors, regardless of the infant's clinical status at

Box 1 Similarities between the US (American Academy of Pediatrics (AAP)) guidelines and the UK (National Institute for Health and Care Excellence (NICE)) guidelines:

1. Both guidelines recommend intrapartum treatment for prevention of early onset GBS infections.
2. Both guidelines identify similar risk factors for early onset sepsis.
3. Neither strategy will identify infected infants with precision, nor avoid treating substantial numbers of infants who are uninfected.
4. Both guidelines recognise the importance of repeated observations in infants with risk factors for sepsis (especially when the decision is made not to treat).
5. Both guidelines recommend stopping antibiotics at 36–48 hours, although the stopping criteria are a little different.
6. Both guidelines emphasise the importance of parental education.

the time of birth.[13 14] As the implications of early antibiotic exposure and potential for adverse consequences have been increasingly recognised,[3] these updated guidelines attempt to address the need for alternative methods of evaluation. Implementation of these newer guidelines has been met with challenges, which vary based on the resources available in each unit.

NICE guidelines versus AAP Committee on Fetus and Newborn guidelines

The UK[11] and the USA[12] have published guidelines for managing infants with suspected and proven early onset sepsis. The UK (NICE) guidelines were updated in April 2021 and the US AAP guidelines were published in December 2018. Given the recent publication dates, both tools need validation in a larger number of populations and settings. The primary aims of the AAP and NICE guidelines are to identify infected infants with precision and to minimise the use of antibiotics in infants who are uninfected. There are similarities and distinctions between both sets of recommendations (box 1). It is noteworthy that neither set of recommendations will identify all infected infants in the first hours of life.

NICE guidelines: commentary

The updated guidelines represent an authoritative and carefully written document based on a careful review of the literature through 2020. The NICE guideline uses 'red flags' and other 'non-red flag' risk factors and clinical indicators to identify which infants require a sepsis evaluation and treatment.[11] In babies with one red flag or two or more 'non-red flag' risk factors, the recommendation is to start antibiotics as soon as possible (after a blood culture has been taken). In a baby without any 'red flags' and only one risk factor or clinical indicator, clinical judgement should be used. If an infant is not treated, the NICE guidelines recommend observation for 12 hours using a newborn 'early warning system.' Unfortunately, the 'early warning system' is not explicitly defined and no recommendation is made for documentation of clinical findings. Twelve hours of observation is probably not sufficient for the subset of infants with sepsis, who become symptomatic at a later time point.[15] The NICE guideline published in 2021 has not been evaluated prospectively nor compared with the sepsis calculator.

AAP guidelines: commentary

The AAP guideline offers three alternative strategies for the management of infants with suspected sepsis: categorical risk assessment, multivariate risk assessment (sepsis calculator) and risk assessment based on the infant's clinical condition using serial observations.[12] Each of these approaches has strengths and limitations. The sepsis calculator is the most often used strategy in the USA and has been incorporated into clinical practices throughout the world. It uses continuous and categorical variables (as described below) and the infant's clinical condition in the first 6–12 hours of life to estimate the risk of sepsis. Blood culture and enhanced clinical observations are recommended for infants with a risk of early onset sepsis ≥1/1000 and empirical antibiotics for infants with an estimated risk of sepsis ≥3/1000. Use of the sepsis calculator has been shown to reduce the use of antibiotics, laboratory testing and admission to the intensive care unit[16] but misses a substantial proportion of infants with EOS.[15] The serial observation approach has also been shown to reduce the use of antibiotics but is labour intensive.[17] Categorial risk assessment as outlined in the AAP guideline is considered by many to be a suboptimal strategy.

Sepsis calculator versus serial observations

Proponents of using either the sepsis calculator or serial observations hope to identify infected neonates at the earliest possible time point and avoid overtreatment of uninfected infants. However, given the limitations of physical examination and inaccuracies in historical data, neither approach can successfully achieve this goal. The sepsis calculator estimates EOS risk using a regression model that includes both categorical variables (GBS status, maternal intrapartum antibiotic therapy and intrapartum prophylaxis) and continuous variables (highest intrapartum maternal temperature, gestational age, duration of ruptured membranes) in infants ≥34 week's gestation.[3] The risk of sepsis per 1000/live births is further quantified with consideration of the infant's clinical condition after birth, classified as well appearing, equivocal or clinical illness.[18 19] Multiple studies have confirmed that implementation of the sepsis calculator has significantly decreased lab sampling and antibiotic use in low-risk infants without adverse outcomes.[20–23]

While the sepsis calculator provides meaningful guidance on decision making for antibiotic use in daily practice, it comes with the important caveat that not all infants who will ultimately develop EOS can be identified using the sepsis calculator in the first hours of life. That is not surprising given that a substantial proportion of infants with EOS will be asymptomatic and risk factors may be incorrectly identified (eg, exact timing of rupture of membranes or maternal colonisation with group B *Streptococcus*). It is clear that use of maternal risk factors combined with an examination at birth can be helpful in assigning EOS risk; however, even infants identified as low risk require continued vigilance and careful evaluation. A systematic meta-analysis of the sepsis calculator found that routine newborn care was initially recommended by the calculator for 44% of infants with proven EOS.[15] Therefore, a process for clinical monitoring of well-appearing infants who do not meet criteria for higher-level evaluation at birth must be coupled with implementation of the sepsis calculator.[24]

The Committee on Fetus and Newborn recommends the serial observation approach as an alternative to the use of the

sepsis calculator. However, there are significantly fewer reports of successful implementation of the serial observation strategy. The concept of serial physical examinations provides a system of structured exams and vital sign monitoring through the first 48 hours of life for well-appearing infants delivered with perinatal risk factors.[25] The frequency of exams should be highest in the first 24 hours after birth, which correlates with the timing of presentation for most infants who develop EOS. Using this approach, several investigators have reported significant reductions in both antibiotic exposure and laboratory testing when compared with previous practice based on categorical risk assessment. It is important to note that implementation of a strategy based on serial exams requires an individualised approach at each centre to succeed.

There is limited information on direct comparisons between the sepsis calculator and serial clinical observations. When applied retrospectively to a cohort of well-appearing infants born to women with chorioamnionitis, the sepsis calculator would have recommended empirical antibiotic therapy in 23.1% of infants based on historical risk factors, compared with 11.6% of infants managed with serial observations.[26] Once the infant's clinical findings over the first 24 hours of life were incorporated into the sepsis calculator, there was improved agreement between the methods with similar recommendations for antibiotic use. In another retrospective analysis of 384 infants who received empirical antibiotics at birth, the sepsis calculator recommended antibiotics in 57%, while the approach using serial clinical exams recommended antibiotics in 17%.[27] Every infant with culture-confirmed EOS would have received antibiotic therapy with both methods. However, both approaches require protocols for clinical monitoring and communication between providers to ensure safe implementation.

Blood culture and diagnosis

EOS is a challenging diagnosis, as there is significant overlap between clinical signs of sepsis and transitional physiological patterns seen in infants following delivery. Moreover, bacteraemia can occur in neonates without any clinical signs or symptoms.[28] Currently, the isolation of a microorganism from a sterilely obtained blood culture is the gold standard for confirming a diagnosis of neonatal sepsis.[29 30] Modern bacterial culture methodologies use a medium which contains antimicrobial neutralisation resins.[31] These systems are reliable when an adequate blood volume is obtained and have consistently been able to detect bacteraemia at a level of 1–10 colony forming units (CFUs) per mL.[12]

Volume of blood culture

Several studies have explored the optimal blood volume required for reliable culture results. In a prospective controlled trial assessing blood volume for pathogen recovery, Yaacobi *et al* found that obtaining 1 mL of blood and dividing it into two bottles of 0.5 mL each (aerobic and anaerobic) significantly improved the isolation of pathogens when compared with inoculating 1 mL of blood into one aerobic bottle (94.4% vs 77.8%, p=0.012).[32] In an in vitro study, Schelonka *et al* observed that with low colony count bacteraemia (<4 CFU/mL), a blood volume of 0.5 mL was insufficient for microorganism recovery, and at least 1 mL should be targeted.[33] Moreover, in a recent study from Woodford *et al*, in which blood culture bottles were weighed after inoculation with blood, 93.4% of blood cultures contained at least 1 mL.[34] In 2018, The AAP Committee on Fetus and Newborn and the Committee on Infectious Diseases concluded that a minimum of 1 mL of blood is required for optimal recovery of pathogens.[5 12]

Effect of maternal intrapartum antibiotic prophylaxis

Antibiotics used as intrapartum antibiotic prophylaxis (IAP), most commonly ampicillin, penicillin and cefazolin, have all been shown to cross the placenta and reach blood levels above the minimum inhibitory concentration for GBS in the fetus and newborn.[35] While the advent of IAP has been life-saving and instrumental in preventing morbidities associated with GBS sepsis, concerns have been raised regarding the effect of IAP on neonatal blood culture accuracy, specifically when detecting low colony count bacteraemia.[10 12 36] However, modern culture systems, which contain resins that deactivate antibiotic agents can reliably detect very low colony counts (1–10 CFU/mL).[12 37 38] Additionally, IAP does not affect the time to positivity when using contemporary blood cultures.[39–41] Therefore, clinicians should be reassured that antibiotics can safely be discontinued when the blood culture is negative in an asymptomatic infant.

Adjunct laboratory tests for diagnosing neonatal sepsis

There has been a lot of research looking into additional diagnostic laboratory testing for neonatal sepsis including haematological counts and acute phase reactants. The challenges with such data include a lack of age-appropriate reference ranges for indices and the non-specific elevation of these markers in situations of stress other than sepsis. With the declining and very low incidence of EOS, the positive predictive values of these diagnostic tests are poor, providing very little diagnostic utility.[13 29]

Leucocyte count and differential count

Newman *et al* conducted a large multicentre retrospective cross-sectional study analysing 67 623 leucocyte and blood culture pairs in infants born at ≥34 weeks' gestation to assess the utility of leucocytes in predicting EOS after birth. The authors found that the indices increased in the first 4 hours of life, with little diagnostic information beforehand. These authors also concluded that when the leucocyte count and absolute neutrophil count (ANC) were extremely low (ANC <1000/uL or leucocyte <5000/uL), there was an increased positive likelihood ratio but persistently low sensitivity.[42] In a subsequent larger multicentre cohort study analysing 166 092 preterm and term neonates with suspected EOS, Hornik *et al* yielded similar conclusions as Newman *et al* with poor sensitivities of low leucocyte count, low ANC and high immature-to-total neutrophil ratios.[43] Other studies have yielded consistent results.[28 44]

Acute phase reactants

As with leucocyte count, acute phase reactants including C reactive protein (CRP) and procalcitonin (PCT) have been evaluated as diagnostic tools when assessing neonates for EOS. Both CRP and PCT are inflammatory markers that are increased secondary to stressful stimuli. CRP is produced by the liver and tends to increase 6–8 hours after onset of illness. As a result, there is little utility in obtaining early CRP levels when deciding on antibiotics for sepsis. Lacaze-Masmonteil *et al* evaluated the usefulness of a single CRP measurement at 18 hours of age in neonates with suspected EOS. These authors found that the sensitivity of a single CRP value for proven sepsis was 64% (95% CI 53 to 59) with a positive predictive value of only 14% (95% CI 11 to 17).[45] However, if serial CRP values remain normal, there is a low likelihood of infection with a negative predictive value of nearly 100%[46] The 2021 NICE guidelines recommend use of

Box 2 Differences between the US (American Academy of Pediatrics (AAP)) guidelines and the UK (National Institute for Health and Care Excellence (NICE)) guidelines:

1. NICE guidelines address the management of both term and preterm infants, whereas the AAP published separate reports for infants ≥35 weeks' gestation and ≤34$^{6/7}$ weeks' gestation.[5]
2. NICE guidelines are likely to be superior in identifying asymptomatic infants with early onset sepsis (EOS) at the moment of birth but result in greater use of antibiotics than the sepsis calculator.[20 48]
3. NICE guidelines divide risk factors for EOS into 'red flag' and 'non-red flag' indicators. This is in contrast to the sepsis calculator, where the relationship of each variable to the outcome of sepsis was analysed separately and then combined into a multivariate model.
4. NICE guidelines use adjunct laboratory testing (eg, C reactive protein) to make clinical decisions and to determine the duration of treatment, while the US sepsis guidelines state that evaluation of inflammatory markers should not determine which infants need antibiotics.
5. NICE guidelines offer the sepsis risk calculator as an alternative strategy, but only in the context of a research or audit project.
6. AAP guidelines recommend the sepsis calculator as one of three principal strategies.
7. NICE guidelines are more liberal with their indications for lumbar puncture and recommend a lumbar puncture where there is strong clinical suspicion of neonatal infection or there are clinical symptoms or signs suggesting meningitis. AAP guidelines recommend a lumbar puncture in infants with positive blood cultures or critical illness.
8. The choice of empirical antibiotics differs between the UK (benzylpenicillin and gentamicin) and US (ampicillin and gentamicin) guidelines.

serial CRP determinations to decide on the duration of antibiotic treatment, while the AAP guidelines do not make that recommendation (see box 2).

Similar to CRP, PCT serum levels begin to rise at around 4–6 hours from the time of illness. As with CRP, PCT can continue to increase up to 48 hours postpartum and can be elevated with a variety of other conditions.[44] In a multicentre trial assessing whether PCT-guided decision making would reduce antibiotic therapy in neonates with suspected EOS, the authors found a significant reduction in duration of antibiotic therapy and length of hospital stay when using PCT as a deciding factor for antibiotic discontinuation.[47] These studies suggest that if the clinician decides to obtain acute phase reactants, they should be obtained serially and at a later time from the onset of infection (6–12 hours). While it can certainly provide reassurance for the discontinuation of antibiotics if levels remain normal, there is little evidence to continue antibiotics purely based on elevated CRP or PCT, when blood cultures remain negative, and the infant is recovering.[29 44]

CONCLUSION

Neonatologists must continue pursuing a comprehensive understanding of EOS, so that we can better diagnose and manage this disease process. The expert guidelines highlighted in this review provide an evidence-based framework for approaching at-risk infants and allow for a more limited and standardised approach to antibiotic use. While these guidelines have significantly reduced antibiotic utilisation worldwide, each unit must individualise their approach to EOS based on the neonatal population they serve and available resources. As advancements in EOS research continues and limitations with sepsis prediction tools are addressed, it is inevitable that our risk stratification and management guidelines will become more precise in the coming years.

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