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EASILY MISSED?

Neonatal sepsis

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What you need to know

- The most common early signs of sepsis in infants are fever or hypothermia, tachypnoea, lethargy, or new parental reports of poor feeding. Consider sepsis in infants with an apparent change in mental status, tone, or perfusion as well
- Neonatal sepsis can present with subtle signs but can rapidly progress to multisystem organ failure and meningitis, which carry high mortality and morbidity rates. Refer infants in whom sepsis is suspected to an emergency department for evaluation
- Although non-specific tests such as a complete blood count and inflammatory markers are often obtained in the initial assessment, the most important test is a blood culture with at least 1 mL of blood, drawn before administering antibiotics

*A 10 day old, full term baby is referred to the emergency department by his paediatrician for tachypnoea and decreased breastfeeding. He was born by uncomplicated vaginal delivery and was discharged home after an uneventful stay in the hospital nursery. Mother and baby established breastfeeding easily and he had been feeding well, every two to three hours. However, since around midnight, his mother reports him as sleepy and difficult to feed. He has had no urine output for six hours. His paediatrician reported tachypnoea with a respiratory rate of 80 breaths per minute and nasal flaring. His blood glucose was 55 mg/dL (3 mmol/L), and he had a rectal temperature of 36.5°C. In the emergency department, he receives a lumbar puncture and has a blood culture drawn, and he is started on ampicillin and ceftriaxone. Eleven hours later, his blood culture returns positive for *Streptococcus agalactiae* (group B *Streptococcus*, or GBS).*

What is neonatal sepsis?

Neonatal sepsis, or illness caused by systemic bacterial infection, is a major cause of paediatric morbidity and mortality. The 2015 Global Burden of Disease study identified neonatal sepsis as the third most common cause of newborn mortality (336 300 total deaths per year) and the 16th greatest contributor to years of lost life across all age groups.¹

Neonatal sepsis is divided into early and late onset forms that differ by mode of acquisition and, thus, time of onset. Early onset sepsis (EOS) is the result of vertical bacterial transmission from the mother during the perinatal period. Antenatally, bacteria can reach the fetus by ascending from the vagina into the uterus, haematogenously through the placenta, or rarely from retroperitoneal acquisition through the fallopian tube.² More commonly, vaginal bacteria seed the fetal mucous membranes, lungs, or intestines during fetal passage through the birth canal.³

Late onset sepsis (LOS), in contrast, results from postnatal environmental exposure to pathogenic bacteria.⁴ Disagreement exists in the literature about the cut off point between EOS and LOS; some sources use 72 hours, some use seven days.⁵⁻⁷ Incidence of LOS is higher in premature infants.⁸ The composition of the newborn microbiome is highly variable, potentially allowing normally harmless commensal microbes to become dominant and to overwhelm to the infant's immune system.⁴ Reflecting their different modes of pathogenesis, different bacteria are typically isolated in EOS compared with LOS, but with considerable overlap (table 1).

Table 1 | Major microbial causes of neonatal sepsis (grouped by frequency)⁵⁻⁷

| Early onset sepsis | Late onset sepsis |
|-------------------------------|----------------------------------|
| Group B <i>Streptococcus</i> | Coagulase-negative staphylococci |
| <i>Escherichia coli</i> | <i>Staphylococcus aureus</i> |
| <i>Streptococcus viridans</i> | <i>Enterococcus</i> spp |
| <i>Enterococcus</i> spp | Group B <i>Streptococcus</i> |
| <i>Staphylococcus aureus</i> | Enterobacter spp |
| Group A <i>Streptococcus</i> | <i>Escherichia coli</i> |
| <i>Haemophilus</i> spp | <i>Pseudomonas</i> spp |

This is one of a series of occasional articles highlighting conditions that may be more common than many doctors realise or may be missed at first presentation. The series advisers are Anthony Harnden, professor of primary care, Department of Primary Care Health Sciences, University of Oxford, and Dr Kevin Barraclough, School of Social and Community Medicine, University of Bristol. You can read more about how to prepare and submit an Education article on our Instructions for Authors pages: <https://www.bmj.com/about-bmj/resources-authors/article-types>

Clinically, EOS and LOS present with the same constellation of features. In both, an early phase of mild and easily missed signs will—if left untreated—progress to severe illness with vital sign instability, central nervous system manifestations such as irritability, lethargy, or seizures, and, ultimately, multi-organ system dysfunction and failure. The time from disease onset to end stage manifestations can be swift—over several hours—or the infant may have simmering mild signs that last up to a day or more before becoming unstable.³

Why is it missed?

Neonatal sepsis is missed because the initial signs are variable and can be subtle to both parents and healthcare practitioners. Furthermore, while some risk factors can raise the likelihood of sepsis, such as maternal rectovaginal GBS colonisation, these correlations are weak. Insidious, sporadic onset is the norm, requiring a high degree of vigilance.

EOS in particular can mimic the normal postnatal transition to the extra-uterine environment, which can involve tachypnoea, accessory muscle use during respiration, and low blood glucose. Clinicians rely on serial observations and perinatal risk factors that are neither sensitive nor specific to identify potentially infected patients. In a study of 240 newborns with risk factors for sepsis, only two of the 12 patients with true-positive blood cultures presented with signs and symptoms of sepsis, while the remaining 10 were asymptomatic, highlighting the challenge of identifying infected neonates.⁹

Although 95% of EOS cases are diagnosed in the first 48 hours after birth, providers can still miss sepsis or, alternatively, overtreat with empiric antibiotics given wide practice variability.¹⁰ A survey was conducted at 81 sites to compare sepsis evaluation and management practices towards term infants who appeared well and were born to mothers with suspected chorioamnionitis. In this survey, clinical practices varied widely: the same infant may receive no evaluation,

a limited laboratory evaluation, or require admission to the neonatal intensive care unit for intravenous antibiotics, depending on the delivery hospital.¹¹ Only 60% of the sites surveyed used national guidelines, while others used locally derived guidelines.

Why does this matter?

Neonatal sepsis results in high rates of morbidity and mortality. Families whose infants die or experience long term complications of missed infections report enormous grief and regret.¹² The neonatal sepsis case fatality rate is 2% in term infants, 20% in premature infants, and 30% in those with concomitant meningitis.¹³⁻¹⁶ In a US based surveillance study of infants with GBS sepsis, 7% of infants with EOS had confirmed meningitis, while 27% of infants with LOS developed meningitis.¹⁷ Regardless of central nervous system infection, neonatal sepsis is associated with multiple forms of developmental delay among survivors.¹⁸

How is it diagnosed?

Clinical features

The signs of neonatal sepsis are variable; therefore any infant with abnormal vital signs, abrupt decline in feeding, apparent change in mental status, tone, or perfusion warrants investigation for sepsis. The most commonly encountered early signs are fever, tachypnoea, lethargy, and poor feeding.¹⁹ However, both a hypothermic baby with a low respiratory rate and an inconsolable, tachycardic newborn brought to the emergency department because he won't take a bottle warrant consideration of sepsis. Respiratory distress in infants may present as grunting, nasal flaring, accessory muscle use, and/or paradoxical breathing. [Table 2](#) lists the most common presenting signs of neonatal sepsis, which are evident in both EOS and LOS. Most perinatally infected infants develop signs of EOS within six hours of birth^{20,21}; LOS can occur at any time in the first three months.⁶

Table 2 | Neonatal sepsis: major presenting clinical findings^{9 10 15 19}

| Category | Signs |
|------------------|--|
| Respiratory | Respiratory distress (tachypnoea, nasal flaring, grunting, retractions), hypoxaemia requiring supplemental oxygen |
| Cardiac | Tachycardia, hypotension, delayed capillary refill, diminished pulses |
| Gastrointestinal | Decreased feeding (refusal of bottle, poor latch after established breastfeeding, excessively long feeding times, fussiness or lack of alertness with feeds), vomiting, abdominal distension |
| Neurological | Irritability, high pitched cry, hypotonia or hypertonia, seizures, apnoea, lethargy or encephalopathy, bulging fontanelle, temperature instability |
| Renal | Oliguria |
| Haematological | Jaundice in the absence of other known risk factors for hyperbilirubinaemia, petechiae or bleeding suggestive of coagulopathy |
| Dermatological | New onset rash, vesicles, erythema or swelling around joints, mottled skin |

Investigations

Infants presenting with any of the signs in [table 2](#) should be considered possibly septic, barring other explanatory diagnoses (such as an injury leading to tachycardia). Neonatal sepsis is a medical emergency, requiring prompt administration of intravenous antibiotics and supportive care in a hospital setting.

The cornerstone of the sepsis investigation is a blood culture drawn after a sterilising skin preparation, to be obtained before administering antibiotics. Modern, automated blood culture detection systems are 100% accurate as long as there are at least 1-2 viable bacterial colony forming units (CFU) in the sample and a

sufficient volume of blood is drawn.²² Up to 25% of infected infants have low concentration bacteraemia with less than 4 CFU/mL of blood, however,²³ and blood culture volumes of at least 1 mL maximise the probability of growth in cases where the bloodstream bacterial burden is low.²²

Diagnostic tests other than blood culture have poor positive predictive value and are not helpful in deciding which newborns require antibiotic treatment, but can expand the clinical picture. A complete blood count is also recommended, in particular for the leucocyte and platelet counts, as well as the leucocyte differential. The leucocyte count has a better predictive value if low (<5000/ μ L)

or high (>40 000/ μ L), but a normal leucocyte count should not reassure against infection.¹⁹ Thrombocytopenia is a frequent finding in neonatal sepsis, but is non-specific. A normal platelet count does not rule out the diagnosis. An immature-to-total (I:T) neutrophil ratio has greater sensitivity compared with the absolute neutrophil or band count. However, the I:T ratio may be elevated in 25%-50% of uninfected infants.¹⁹

Inflammatory markers are also non-specific but can be drawn at the time of the blood culture to set a baseline value to trend over time. C reactive protein (CRP) is an acute-phase reactant that peaks within 24-48 hours of infection onset. The negative predictive value of two normal CRP values (the first 8-24 hours after birth and the second 24 hours later) is 99.7%; however, an elevated value in the setting of a newborn who appears well with no other risk factors has low specificity for infection and should not automatically warrant antibiotic treatment.^{19 24} Procalcitonin is another acute phase reactant that reaches its peak values earlier than CRP, around 6-12 hours after infection onset.²⁵ Although it has a slightly greater sensitivity than CRP for sepsis, it is less specific, since a physiological rise in procalcitonin occurs in both term and preterm infants during the first few days of life.²⁵

A lumbar puncture is indicated if: 1) the blood culture is positive; 2) the clinical course or laboratory data strongly suggest bacterial sepsis; 3) the infant does not improve with appropriate antimicrobial therapy; or 4) when there are clinical signs referable to the central nervous system such as lethargy, irritability (eg, inconsolable crying), fever, or seizure. If respiratory symptoms are present, a chest radiograph can help detect pneumonia, but infectious radiographic findings can be difficult to distinguish from those of respiratory distress syndrome or transient tachypnoea of the newborn. In the absence of a suspected congenital urogenital abnormality, urine cultures are rarely positive in infants with EOS. Thus urine cultures are not routinely obtained in a standard evaluation for EOS but may be considered when evaluating an infant for LOS.

How is it managed?

The mainstay of treatment for neonatal sepsis is broad spectrum intravenous antibiotics that are narrowed once the pathogen and its antibiotic sensitivity are characterised. Common initial empiric antibiotic combinations are ampicillin plus gentamicin to cover common causes of EOS, or vancomycin plus an aminoglycoside or third generation cephalosporin to cover common causes of LOS; specific regimens vary with local bacterial prevalence and antibiotic resistance patterns. Duration of treatment varies depending on the microbe identified as well as evidence of any underlying infection. Treatment for uncomplicated bacteraemia ranges from seven to 10 days.^{19 26} Supportive care is essential, and might include intravenous fluids and nutrition, pressor medications, phototherapy if hyperbilirubinaemia co-occurs with sepsis, non-invasive or invasive respiratory support, and/or systemic steroids to support blood pressure.

Patient perspective

A patient whom we cared for in our neonatal intensive care unit in New York City grew GBS from his blood culture, had a negative lumbar puncture, and was treated with penicillin G for 10 days. He is now almost six months old and thriving. His parents both remember how unexpected and alarming it was to be told that their newborn had sepsis.

The patient's mother recalls that it was extremely difficult—especially in the setting of postpartum fatigue and while adjusting to being a first time parent—to discern that her newborn was showing signs of illness. She emphasised that his grunting sounds, which were the first manifestation

of infection, could have easily been mistaken for normal newborn noises. She credits her mother and mother-in-law with realising that something was not right and insisting that her son be evaluated.

"I knew nothing about GBS before this happened," she said. "There is a lack of education on this, especially regarding things to look out for. I felt really lucky that my mom and mother-in-law noticed and that the hospital staff reacted right away." The patient's father remembers disbelief as he learned that his son had a serious bacterial infection. He said, "I just kept thinking, 'How is this happening? How was this not stopped?'" He said that reading this review helped ease his concerns by illustrating that, despite extensive public health measures, sporadic neonatal sepsis remains a problem that can only be countered through vigilant attention to early newborn signs of distress. Both parents expressed tremendous relief that there were no serious consequences of the illness, and, during our telephone conversation, our former patient could be heard in the background, cooing contentedly.

Education into practice

- Based on reading this article, what neonatal history or physical examination findings will prompt you to consider sepsis?
- How will you counsel parents regarding signs of neonatal sepsis that would require immediate evaluation by a provider?

How patients were involved in the creation of this article

We interviewed the parents of an infant in our unit who inspired this written piece. They stated their concerns and questions regarding neonatal sepsis and the subtleties behind a diagnosis that can carry significant clinical implications. They were grateful for the vigilance of their family members and our medical staff for establishing the diagnosis quickly and treating it effectively with no untoward consequences to their son. This set the framework for the content of this paper, emphasising how neonatal sepsis can be easily missed and what signs should alert care providers to the possibility of sepsis in future cases.

How this article was created

This article was inspired by a neonate in the nursery who developed subtle respiratory symptoms and was ultimately diagnosed with bacterial sepsis. We reviewed the epidemiology, presentation, and management of sepsis by searching "early-onset neonatal sepsis" and "late-onset neonatal sepsis" in PubMed. We reviewed guidelines by the National Institute for Health and Care Excellence and the American Academy of Pediatrics' Committee on Fetus and Newborn and Committee on Infectious Diseases.

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