Neonatal Infections

Pathophysiology, Diagnosis, and Management

Joseph B. Cantey
Editor

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Preface

If pressed, those of us in the medical profession who are fortunate enough to care for children can produce a variety of reasons why we picked this particular field. If you ask enough people—or read enough personal statements—a few themes recur. Children are rarely to blame for their condition, the odd swallowed quarter aside. Children, by and large, get better over time. And the chance to have an early impact on a long, meaningful, productive life is immeasurably valuable. Neonates are the quintessential pediatric patients—they literally have their entire lives in front of them. All they did to acquire their disease was be born. Too often, though, these infants are born with or soon acquire infection—unwanted stowaway pathogens that these infants neither invited nor deserve. Timely recognition and treatment of these infections can have a major impact on infant survival and quality of life.

Neonatal Infections: Pathophysiology, Diagnosis, and Management is intended as a quick reference guide for the busy clinician caring for newborns and young infants, whether in the nursery, the neonatal intensive care unit, the ward, or the clinic. It covers infections acquired during birth or while in the hospital (Part I) as well as congenital infections (Part II). Summary chapters regarding prevention strategies, including infection control, outbreak management, antibiotic stewardship, and immunizations, are also included (Part III). *Neonatal Infections* is intended to be concise yet thorough and as visual as possible. I am extremely thankful to all of the authors who contributed their time and expertise to this effort. If you find this text useful, as I hope you will, it is because of them.

I am indebted to so many teachers, mentors, and friends who helped me through my training. To Julia McMillan, my residency director at Johns Hopkins—thank you for convincing me to pursue pediatric infectious diseases. To George McCracken, thank you for offering me a fellowship spot in the parking lot of Love Field in Dallas all those years ago. To Pablo J. Sánchez, thank you for being a patient, considerate, wonderful mentor and for convincing me to add a neonatology fellowship—it was just crazy enough to work! Most importantly, thank you to my wife, Leticia Shanley. You are the best pediatrician I know, and without your unwavering support I would be personally and professionally adrift.

And to you, reader—thank you for taking care of newborns. This book is for you… and them.

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J. B. Cantey

Contents

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Part I

Perinatal Infections

Early-Onset Sepsis

Susan A. Lee

Epidemiology

Sepsis is a systemic condition that includes infection of a sterile site with concomitant signs of illness [1]. Blood, urine, and cerebrospinal fluid (CSF) are most commonly evaluated, but other normally sterile sites (e.g., peritoneal, pleural, pericardial, synovial, bone) can also be infected. Neonatal sepsis can be classified by age of onset and timing of the sepsis episode (Table 1). The etiology and management of EOS are distinct from that of late-onset sepsis, which is discussed in detail in chapter "Late-Onset Sepsis."

In the United States, the overall rate of early-onset sepsis is approximately 0.8–1 per 1000 live births [2, 3]. GBS accounts for the greatest proportion of EOS cases (35–40%), followed by *E. coli*. GBS is more common among term infants; *E. coli* accounts for a greater proportion of EOS among preterm infants. However, a wide variety of organisms are capable of causing EOS. *Listeria monocytogenes* has become less common, accounting for <1% of EOS cases.

Risks for EOS include both maternal and neonatal factors (Box 1):

Maternal risk factors. The leading risk factor for EOS is chorioamnionitis. Chorioamnionitis is defined as an intra-amniotic infection that typically results from ruptured membranes allowing for microbial invasion [4]. Approximately 40% of infants with EOS are born to mothers with chorioamnionitis [2, 3]. Chorioamnionitis can be diagnosed clinically or with histopathology, although histopathology is generally not available in time to inform clinical decisions [5]. The duration of rupture

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Table 1 Definitions of early-onset and late-onset sepsis in neonates

	Early-onset sepsis	Late-onset sepsis
Etiology	~40% GBS ~30% *E. coli* ~30% other	1. Coagulase-negative *Staphylococcus* 2. *Staphylococcus aureus* 3. *E. coli* and other gram-negatives 4. GBS and other gram-positives 5. *Candida*
Age of onset	Age ≤ 72 h	Age > 72 h
Time of acquisition	Before or during delivery	After delivery
Mode of acquisition	Perinatal (mother-to-infant transmission)	Postnatal (acquired from hospital environment and community)
Clinical findings	Rapid onset Systemic disease more common than focal infection Bacteremia/pneumonia common	Onset may be slower or fulminant Focal infection (e.g., meningitis, osteomyelitis, urinary tract infection) more likely

Box 1 Risk Factors for Early-Onset Sepsis

Maternal

- Chorioamnionitis
- Intrapartum fever (without chorioamnionitis diagnosis)
- Prolonged rupture of membranes
- Colonization with GBS
- Inadequate intrapartum antibiotic prophylaxis

Infant

- Prematurity
- Low birth weight
- Low Apgar scores
- Need for endotracheal intubation

of membranes is also associated with increased risk for sepsis, largely due to the development of chorioamnionitis. However, prolonged rupture—defined as ≥18 h—is independently associated with increased risk even in the absence of chorioamnionitis.

Infant risk factors. The most important infant characteristic is the degree of prematurity. EOS rates are inversely proportional to gestational age and birth weight, with the highest incidence occurring in the smallest infants.

As discussed below, risk calculators use the presence or absence of these risk factors along with the infant's clinical status to determine the need for evaluation and treatment for EOS [6].

Pathogenesis

Early-onset sepsis can occur one of two ways:

1. In utero infection usually results from ascending bacteria reaching the amniotic fluid and subsequently being aspirated or swallowed by the fetus. Many bacteria, including GBS and *E. coli*, have attachment proteins that allow them to ascend from the birth canal to the amnion. Rupture of membranes facilitates this process by removing a major physical barrier between the fetus and the organisms, but bacteria can invade even with intact membranes. Organisms aspirated in utero cause pneumonia or systemic infection at or shortly after birth. Of note, transplacental transmission of GBS and *E. coli* are rare, but this is the primary route for *Listeria*.
2. Perinatal infection is acquired during the delivery process, either during descent or expulsion of the infant. The risk for perinatal disease is reduced—but not eliminated—by cesarean delivery. Organisms that attach to and colonize the infant during delivery can subsequently invade, with onset of symptoms usually within 24–36 h of delivery.

Clinical Findings

Clinical signs of EOS are very nonspecific (Table 2). Temperature instability (either fever or hypothermia) is the most common finding but is present in less than half of cases. In addition, many noninfectious conditions can mimic the clinical presentation of neonatal sepsis. Noninfectious respiratory conditions such as transient tachypnea of the newborn or respiratory distress syndrome and hypotension secondary to prematurity routinely lead to sepsis evaluations and empiric antibiotic therapy [7–9]. Given the nonspecific presentation and the adverse outcomes associated with delayed therapy, nursery providers should have a relatively low threshold for consideration of sepsis in an ill-appearing infant.

Early-onset sepsis is virtually always rapid in onset, with the vast majority of infants presenting either at delivery or within 24 h. EOS is generally a systemic illness; focal findings are most often limited to pulmonary involvement. Meningitis or other focal compartmental infections are possible but less common than with late-onset sepsis (see chapter “Late-Onset Sepsis”).

The mortality of EOS is approximately 15%; the majority of deaths occur by age 3 days [2, 3]. The case fatality rate of EOS is inversely related to the gestational age. Among survivors of EOS, morbidity is usually limited to those with early-onset meningitis or those who require prolonged mechanical ventilation due to sepsis with a concomitant increased risk for bronchopulmonary dysplasia.

Table 2 Clinical findings of neonatal sepsis

System	Sign
Systemic	• Hyperthermia • Hypothermia • Temperature instability
Pulmonary	• Tachypnea • Grunting • Retractions or nasal flaring
Neurologic	• Apnea • Irritability • Lethargy • Seizures • Hypotonia • Full or bulging fontanelle
Cardiovascular	• Tachycardia • Bradycardia • Hypotension • Poor perfusion • Cyanosis • Pallor
Gastrointestinal	• Poor feeding • Jaundice • Abdominal distention or ileus • Vomiting • Hepatomegaly • Diarrhea
Other	• Petechiae • Purpura • Coagulopathy

Diagnosis

The gold standard to diagnose sepsis is blood culture. A minimum of 1 mL of blood should be obtained [10]. Since EOS is a systemic illness that presents with bacteremia, typically only blood cultures are required when EOS is suspected. This is in contrast to late-onset sepsis, in which sampling of other sites (urine, CSF) is routinely indicated. However, CSF should be obtained for culture and cytology if signs of central nervous system involvement are present (e.g., apnea, seizures) or when blood cultures turn positive. Urine cultures are not indicated.

Non-culture-based ancillary testing, such as complete blood counts with differential, C-reactive protein, procalcitonin, and others, has good negative predictive value but limited positive predictive value. If used, ancillary testing should be used to reassure providers when the infant appears ill, but cultures are sterile. However, abnormal values in an otherwise well-appearing neonate should not prompt initiation or continuation of empiric antibiotic therapy [11].

There are several guidelines to help guide decisions regarding which infants to test and empirically treat for early-onset sepsis. Unquestionably, ill-appearing

Table 3 American Academy of Pediatrics 2012 recommendations for management of infants with suspected early-onset sepsis

Sepsis evaluation	All ill-appearing infants Well-appearing infants IF • Chorioamnionitis-exposed • <37 weeks and either prolonged rupture of membranes or inadequate intrapartum antibiotic prophylaxis
Diagnosis	Blood: Culture of ≥1 mL CSF: Not routinely indicated[a] Urine: Not indicated Ancillary tests[b]: Not routinely indicated but may provide additional negative predictive value
Treatment	Ampicillin and gentamicin Cefotaxime should be restricted to infants with suspected or proven meningitis with gram-negative organism

Adapted from reference 10. *CSF* cerebrospinal fluid
[a]CSF should be obtained if infant has overt signs of central nervous system involvement, if blood cultures identify a pathogen, or those who are critically ill or strongly suspected of having sepsis
[b]White blood cell counts with differential, c-reactive protein, procalcitonin, etc.

infants should be evaluated. For well-appearing infants, the current American Academy of Pediatrics recommendations use maternal and infant-risk factors to determine need for cultures and treatment (Table 3) [10].

Sepsis calculators are multivariable prediction models that estimate the risk of EOS among late preterm and term neonates based on objective data and the neonate's clinical status. This method has been prospectively validated and significantly reduces the number of neonates who require sepsis evaluations and empirical antibiotic therapy relative to existing guidelines without adversely affecting outcomes [6]. However, sepsis calculators have not yet been widely adopted or applied to more preterm infants.

Treatment

Empiric therapy. Ampicillin and gentamicin remain the primary empiric therapy for early-onset sepsis. GBS remains universally susceptible to penicillin, and gentamicin provides good coverage for *E. coli* and other gram-negative causes of EOS. The proportion of ampicillin-resistant *E. coli* has increased markedly over the past several decades, but aminoglycoside resistance has not [12–14]. In addition, the rise in cephalosporin resistance and extended-spectrum-beta-lactamase-producing gram-negative organisms has outpaced aminoglycoside resistance [15, 16]. Therefore, third- and fourth-generation cephalosporins should be reserved for suspected or proven gram-negative meningitis, as gentamicin does not achieve sufficient concentrations in the CSF. Empiric therapy can be discontinued as early as 24–36 h if blood cultures remain sterile.

Definitive therapy. When a pathogen is recovered, treatment should be altered to provide effective coverage with the narrowest possible agent or agents. The use of

two active agents to treat a given organism has not been shown to be beneficial in neonates and is not recommended under usual circumstances [17]. However, when gram-negative rods are identified from the blood of a critically ill infant (e.g., shock, acute respiratory failure), the use of a second agent from a different antibiotic class (e.g., piperacillin/tazobactam and gentamicin) will increase the likelihood that at least one of the agents has activity against the organism and should be considered. Once the speciation and susceptibility of the pathogen is known, therapy should be narrowed to a single agent. The optimal duration of therapy for early-onset sepsis has not been well studied. Treatment recommendations vary by organism and by compartment; gram-negatives are generally treated with longer durations than gram-positive organisms; meningitis is treated for longer than bacteremia alone. At minimum, antibiotics should be continued until cultures are sterile, and the neonate shows clinical recovery [18].

Adjunctive therapy. Currently, adjunctive therapies are not recommended in the treatment of early-onset sepsis. Neutropenia is associated with poor prognosis and mortality in neonatal sepsis. However, studies of therapies aimed at increasing neutrophil concentration—including granulocyte transfusions, granulocyte/macrophage colony-stimulating factor, pentoxifylline, and intravenous immune globulin—have had mixed results [19–22]. Currently, adjunctive therapies are not recommended in the treatment of early-onset sepsis; additional research is required to determine the potential benefit of these strategies.

Prevention

Prevention of EOS requires multiple strategies. Since GBS accounts for the greatest share of cases, prevention of GBS is a priority. Universal screening of pregnant women for GBS colonization and intrapartum antibiotic prophylaxis for colonized women has dramatically reduced the incidence of GBS EOS to the point where late-onset infection (see chapter "Late-Onset Sepsis") is more common [23]. The majority of EOS cases occur when screening is missed or intrapartum antibiotic therapy is not given in time [24]. Optimizing systems will prevent some, but not all, EOS due to GBS [25]. Ultimately, a GBS vaccine might have the most impact on neonatal sepsis rates worldwide [26]. In 2018, the World Health Organization in 2018 issued a statement with research priorities and technical requirements in order to facilitate creation and implementation of an effective GBS vaccine [27].

Another major aspect of prevention of EOS is reduction in preterm deliveries. Prematurity is a major risk factor for EOS, second only to chorioamnionitis. Strategies that reduce preterm delivery, such as prevention of teen pregnancy, comprehensive prenatal care, smoking and drug cessation, 17-hydroxyprogesterone prophylaxis for women with a history of a preterm delivery, and others, would also be expected to reduce early-onset sepsis rates, particularly cases due to *E. coli* and the gram-negatives that are more common among preterm infants [3, 28].

References

1. Shane AL, Sanchez PJ, Stoll BJ. Neonatal sepsis. Lancet. 2017;390:1770–80.
2. Schrag SJ, Farley MM, Petit S, et al. Epidemiology of invasive early-onset neonatal sepsis, 2005 to 2014. Pediatrics. 2016;138:e20162013.
3. Stoll BJ, Hansen NI, Sanchez PJ, et al. Early onset neonatal sepsis: the burden of group B streptococcal and *E coli* disease continues. Pediatrics. 2011;127:817–26.
4. Higgins RD, Saade G, Polin RA, et al. Evaluation and management of women and newborns with a maternal diagnosis of chorioamnionitis: summary of a workshop. Obstet Gynecol. 2016;127:426–36.
5. Wortham JM, Hansen NI, Schrag SJ, et al. Chorioamnionitis and culture-confirmed, early-onset neonatal infections. Pediatrics. 2016;137:e20152323.
6. Kuzniewicz MW, Puopolo KM, Fischer A, et al. A quantitative, risk-based approach to the management of neonatal early-onset sepsis. JAMA Pediatr. 2017;171:365–71.
7. Weintraub AS, Cadet CT, Perez R, et al. Antibiotic use in newborns with transient tachypnea of the newborn. Neonatology. 2013;103:235–40.
8. Shani L, Weitzman D, Melamed R, et al. Risk factors for early sepsis in very low birth weight neonates with respiratory distress syndrome. Acta Paediatr. 2008;97:12–5.
9. Dempsey EM, Barrington KJ. Diagnostic criteria and therapeutic interventions for the hypotensive very low birth weight infant. J Perinatol. 2006;26:677–81.
10. Polin RA. Committee on fetus and newborn. Management of neonates with suspected or proven early-onset bacterial sepsis. Pediatrics. 2012;129:1006–15.
11. Cantey JB, Baird SD. Ending the culture of culture-negative sepsis in the neonatal ICU. Pediatrics. 2017;140:e2017044.
12. Lu Q, Zhou M, Tu Y, Yao Y, Yu J, Cheng S. Pathogen and antimicrobial resistance profiles of culture-proven neonatal sepsis in Southwest China, 1990-2014. J Paediatr Child Health. 2016;52:939–43.
13. Bizzaro MJ, Dembry LM, Baltimore RS, Gallagher PG. Changing patterns in neonatal Escherichia coli sepsis and ampicillin resistance in the era of intrapartum antibiotic prophylaxis. Pediatrics. 2008;121:689–96.
14. Heideking M, Lander F, Hufnagel M, et al. Antibiotic susceptibility profiles of neonatal invasive isolates of *Escherichia coli* from a 2-year nationwide surveillance study in Germany, 2009-10. Eur J Clin Microbiol Infect Dis. 2013;32:1221–3.
15. Downie L, Armiento R, Subhi R, Kelly J, Clifford V, Duke T. Community-acquired neonatal and infant sepsis in developing countries: efficacy of WHO's currently recommended antibiotics – systematic review and meta-analysis. Arch Dis Child. 2013;98:146–54.
16. Greenhow TL, Cantey JB. The disputed champion: ampicillin and gentamicin for febrile young infants. Hosp Pediatr. 2017; Available online Jul 20 2017.
17. Johnson SJ, Ernst EJ, Moores KG. Is double coverage of gram-negative organisms necessary? Am J Heatlh Syst Pharm. 2011;68:119–24.
18. Stockmann C, Spigarelli MG, Campbell SC, et al. Considerations in the pharmacologic treatment and prevention of neonatal sepsis. Pediatr Drugs. 2014;16:67–81.
19. Mohan P, Brocklehurst P. Granulocyte transfusions for neonates with confirmed or suspected sepsis and neutropaenia. Cochrane Database Syst Rev. 2003;4:CD003956.
20. INIS Collaborative Group, Brocklehurst P, Farrell B, et al. Treatment of neonatal sepsis with intravenous immune globulin. N Engl J Med. 2011;265:1201–11.
21. Pammi M, Haque KN. Pentoxifylline for treatment of sepsis and necrotizing enterocolitis in neonates. Cochrane Database Syst Rev. 2015;3:CD004205.
22. Carr R, Brocklehurst P, Dore CJ, Modi N. Granulocyte-macrophage colony stimulating factor administered as prophylaxis for reduction of sepsis in extremely preterm, small for gestational age neonates (the PROGRAMS trial): a single-blind, multicenter, randomised controlled trial. Lancet. 2009;373:226–33.

23. Clifford V, Garland SM, Grimwood K. Prevention of neonatal group B streptococcus disease in the 21st century. J Paediatr Child Health. 2012;48:808–15.
24. Vergnano S, Embleton N, Collinson A, Menson E, Russell AB, Heath P. Missed opportunities for preventing group B streptococcus infection. Arch Dis Child Fetal Neonatal Ed. 2010;95:F72–3.
25. Van Dyke MK, Phares CR, Lynfield R, et al. Evaluation of universal antenatal screening for group B streptococcus. N Engl J Med. 2009;360:2626–36.
26. Baker CJ. Vaccine prevention of group B streptococcal disease. Pediatr Ann. 1993;22:711–4.
27. Vekemans J, Moorthy V, Friede M, et al. Maternal immunization against Group B streptococcus: World Health Organization research and development technological roadmap and preferred product characteristics. Vaccine. 2018; Available online Feb 2 2018.
28. Shapiro-Mendoza CK, Barfield WD, Henderson Z, et al. CDC grand rounds: public health strategies to prevent preterm birth. MMWR Morb Mortal Wkly Rep. 2016;65:826–30.

Late-Onset Sepsis

Niraj Vora

Epidemiology

Late-onset sepsis (LOS) is defined as infection of a sterile site (e.g., blood, urine, cerebrospinal fluid [CSF]) after age 72 h [1, 2]. The only exception is that the current definition of late-onset group B *Streptococcus* (GBS) infection begins after age 7 days, with the first week of life being considered early-onset sepsis [3]. The primary risk factor for LOS is prematurity; the most preterm infants are at highest risk for LOS. Approximately 25–30% of extremely low birth weight (ELBW, <1000 g) infants will have LOS during their NICU stay [1, 4]. This number decreases to about 10–15% for infants 1001–1500 g birth weight and to <2% for infants >1500 g birth weight [2, 5, 6].

The organisms responsible for LOS vary over time and between locations. Yale New Haven Hospital has produced a series of reports describing the changing patterns of organisms responsible for LOS from 1928 to 2003 showing the evolution of LOS over almost a century [7–12]. Prior to introduction of antibiotics in the 1930s and 1940s, gram-positive cocci, including *Staphylococcus aureus* and *Streptococcus pyogenes* (group A strep), were responsible for the majority of neonatal sepsis. Once antibiotics were introduced, gram-negative enteric bacilli such as *Escherichia coli* became the leading cause of serious infections in newborn.

However, over the last several decades, coagulase-negative *Staphylococcus* (CoNS) species have emerged as the most commonly identified organism in LOS (Table 1). This may be due to increased survival of the most preterm infants and a concomitant increase in reliance on indwelling catheters and other medical devices. Other gram-positives such as *S. aureus*, GBS, *Enterococcus*, and others; gram-negatives including *E. coli* and other coliforms; *Pseudomonas*, *Serratia*, and others;

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Table 1 Organisms associated with late-onset sepsis and their approximate prevalence

Organism	Frequency
Gram-positives	75%
Coagulase-negative staphylococci	60–70%
Staphylococcus aureus[a]	10%
Group B streptococci	3–5%
Enterococcus sp.	3–5%
Group A streptococci	1–2%
Gram-negatives	20%
Escherichia coli	5–7% each
Klebsiella	
Enterobacter	
Citrobacter	1–2% each
Pseudomonas	
Serratia	
Others	
Candida sp.	5%

[a]In the United States, approximately 75% of isolates are methicillin-susceptible and 25% are methicillin-resistant, but proportion varies between neonatal intensive care units

and fungal species (primarily *Candida*; see chapter "*Candida*") are frequently encountered causes of LOS [1–6].

Pathogenesis

LOS has a distinct pathogenesis compared with early-onset sepsis (Table 2). In contrast to early-onset sepsis, which is acquired during the perinatal period (see chapter "Early-Onset Sepsis") and is caused by organisms common to the delivery tract such as GBS or *E. coli*, LOS is caused by acquisition of pathogenic organisms during the postnatal period, colonization, and subsequent invasion [13]. These differences manifest as later presentation (hence the 72 h cutoff between early-onset and late-onset sepsis) and a broader range of causative organisms. Horizontal transfer of pathogenic bacteria on contaminated hands or medical equipment leads to either immediate invasion (e.g., if bacteria are infused in a contaminated infusion or procedure) or colonization of the skin, mucous membranes, or gastrointestinal tract. Colonized infants can then develop subsequent invasion either by autoinoculation (e.g., if their stool comes in contact with a central catheter hub) or translocation directly into the bloodstream [14]. Unsurprisingly, therefore, the causative organism of LOS is often one that the infant is already colonized with [15].

Once an organism reaches the bloodstream, it can cause a nonspecific sepsis syndrome or it can localize to one or more body sites and cause focal infection. In addition, some cases of LOS are caused by direct infection of a body site without preceding bacteremia; examples include ascending urinary tract infection, direct

Table 2 Early-onset versus late-onset sepsis in neonates and young infants

	Early-onset sepsis	Late-onset sepsis
Etiology	~40% GBS ~30% *E. coli* ~30% other	1. Coagulase-negative *Staphylococcus* 2. *Staphylococcus aureus* 3. *E. coli* and other gram-negatives 4. GBS and other gram-positives 5. *Candida*
Age of onset	Age ≤ 72 h	Age > 72 h
Time of acquisition	Before or during delivery	After delivery
Mode of acquisition	Perinatal (mother-to-infant transmission)	Postnatal (acquired from hospital environment and community)
Clinical findings	Rapid onset Systemic disease more common than focal infection Bacteremia/pneumonia common	Onset may be slower or fulminant Focal infection (e.g., meningitis, osteomyelitis, urinary tract infection) more likely

inoculation of skin or soft tissue during phlebotomy, or ventilator-associated pneumonia.

Clinical Findings

The initial signs of LOS are often subtle and nonspecific such as decreased activity, poor feeding, lethargy, apnea, fever or hypothermia, respiratory distress, and jaundice [16, 17]. As a result, sepsis evaluations are often performed when clinical changes are detected, since virtually every finding has been associated with sepsis. In an effort to improve specificity, clinical prediction models that use trends in vital signs, propensity scores, or laboratory values have been used with varying degrees of success [18–20]. In some cases, more specific localizing findings may be present (Table 3). For example, osteomyelitis may present with pseudoparalysis or irritability with movement of the affected limb. Skin and soft tissue infections can present with skin changes or swelling. Meningitis may present with seizures. However, focal infection is possible even when localizing signs are absent [21].

Diagnosis

The diagnosis of LOS based solely on clinical signs is not possible due to the nonspecific nature of the presentation [22]. The gold standard for diagnosis is isolation of a pathogen from a normally sterile site (blood, CSF, urine, pleural or peritoneal fluid, bone or joint aspirate) [23]. For non-sterile sites such as the upper respiratory tract or the skin, culture remains critical but should be used in conjunction with clinical findings and pretest probability of sepsis.

Table 3 Clinical findings, approach to diagnosis, and treatment of common systemic and focal manifestations of late-onset sepsis

Condition	Clinical findings	Diagnosis	Antibiotic treatment[a]
Bacteremia	• Decreased activity • Poor feeding • Lethargy • Hypotension • Apnea, bradycardia, or desaturations • Temperature instability • Respiratory distress or failure • Jaundice • Leukopenia or leukocytosis • Thrombocytopenia • Anemia	• Blood culture	7–10 days
Meningitis	• Similar to bacteremia AND: • Seizures • Lethargy/unresponsiveness • Bulging fontanelle • Nuchal rigidity	• Cerebrospinal fluid culture	14–21 days
Urinary tract infection	• Similar to bacteremia	• Urine culture	7–10 days
Osteomyelitis or septic arthritis	• Decreased movement • Pseudoparalysis • Irritability with passive movement • Swelling or redness	• Blood culture • Bone or joint fluid culture • Radiographic changes	21–42 days
Pneumonia	• Respiratory deterioration or failure • New findings on chest radiographs • Changes in sputum	• Endotracheal tube culture[b] • Radiographic changes	5–7 days
Skin and soft tissue	• Redness • Swelling • Drainage • Induration or fluctuance	• Wound culture[b]	Drainage procedure and antibiotics until clinical findings resolve (5–7 days)

[a]Treatment durations are guides only; duration of therapy should take into consideration infant's clinical status, response to therapy, persistence of any infected material, etc.
[b]Culture of non-sterile sites such as upper airway and skin should be interpreted with caution

Cultures

Blood culture. A blood sample of at least 1 mL ensures excellent sensitivity [24]. Sending two cultures from two different sites will help to differentiate contaminants (e.g., if CoNS grows in one culture but not the other) but requires a second blood draw and does not improve sensitivity compared to an equal volume of blood obtained from a single site. Of note, *Candida* will grow in regular blood culture media; specific fungal cultures are not required.

Urine culture. Urine culture should be obtained in all cases of suspected LOS; 5–10% of LOS cases are due to isolated urinary tract infection [25, 26]. Urine should be obtained by catheterization or suprapubic aspiration; bag specimens are frequently contaminated. The value of urinalysis in preterm infants has not been well studied, but the absence of leukocyte esterase, nitrites, or pyuria does not preclude the possibility of UTI in preterm infants [27].

Cerebrospinal fluid culture. Lumbar puncture for CSF analysis and culture is critical for infants with suspected LOS. Approximately 5% of infants with LOS have associated meningitis, and one-third of infants with meningitis have sterile blood cultures [21, 28]. Therefore, if blood cultures alone are utilized, cases of meningitis will inevitably be missed [29, 30]. Meningitis requires different antimicrobial therapy and a longer duration of treatment than other LOS, and therefore determining the presence or absence of meningitis is a critical step in the evaluation of LOS.

Endotracheal tube cultures. Endotracheal tubes are rapidly colonized by normal upper airway flora shortly after placement [31]. Therefore, detection of bacteria from endotracheal tube culture may represent either colonization or infection. When the pretest probability of lower respiratory tract disease is low (e.g., when another source of infection is likely or in the absence of radiographic or clinical changes), positive tracheal cultures are virtually worthless. Therefore, endotracheal tube cultures should only be considered when both clinical and radiographic findings are suggestive of pneumonia. In contrast, bronchoalveolar lavage specimens from the lower respiratory tract would be expected to be sterile and therefore are more helpful. However, bronchoalveolar lavage is not routinely available for preterm infants in most centers.

Skin cultures. As with the upper airway, the skin is not sterile. Normal cutaneous flora includes CoNS, *Corynebacterium* and other diphtheroids, and other gram-positives. Colonization with potential pathogens including group A streptococci, *S. aureus*, and *Candida* can also be identified and must be differentiated from active infection [32]. Interpretation of culture results should be done in consideration of the infant's clinical status.

Other cultures. Other sterile sites can be sampled for culture under specific situations. Infants with suspected bone or joint infections can undergo percutaneous aspiration of bone or synovial fluid [33]. Peritoneal fluid can be obtained during drain placement or laparotomy. Pericardial or pleural fluid may be obtained during drainage procedures. In general, fluid should be sent for cytology, gram stain, and culture whenever infection is suspected; providing as much detail as possible to the microbiology lab regarding patient history and sample source will ensure that the cultures are processed appropriately.

Non-culture-Based Microbiologic Tests

PCR and nucleic acid-based testing, rapid antigen detection, direct fluorescent antibody testing, and other similar tests may be available. These tests vary in terms of

sensitivity and specificity and at present do not preclude the need for bacterial cultures. PCR in particular is becoming increasingly prevalent. Benefits to PCR include its impressive sensitivity and rapid turnaround time. However, PCR testing of blood or spinal fluid has been associated with false-positive results. PCR will also detect dead bacteria that has been previously treated or resolved, which may prompt additional, unnecessary antibiotic therapy [34]. As PCR is increasingly used and studied, our understanding of how it fits into the clinical management of these infants will grow.

Ancillary Laboratory Testing

Ancillary lab tests such as white blood cell counts and differentials, C-reactive protein, procalcitonin, and others are often used to determine an infant's risk for infection. Although these tests have been relatively well-studied for suspected early-onset sepsis, validation for late-onset sepsis has not been as robust. In most cases, the normative values for age <72 h have been extrapolated out to older ages. The evidence suggests that these ancillary tests have reasonably good negative predictive value but poor positive predictive value [35, 36]. This means that normal ancillary testing will support discontinuation of antibiotic therapy in an infant with sterile culture results. However, abnormal laboratory tests should not be used as a reason to extend therapy for children with sterile culture results, particularly if their clinical findings are resolved or improving.

Treatment

Empiric Therapy

Since sepsis has significant clinical implications and can progress rapidly, empiric antimicrobial therapy should be initiated promptly when LOS is suspected. An understanding of local epidemiology (for the patient in question, within the nursery, and within the hospital or community) is essential in order to choose appropriate empiric therapy. In general, empiric therapy for LOS should include coverage against common hospital-acquired organisms such as *S. aureus* and gram-negative enteric bacilli (Fig. 1). The use of empiric antifungal therapy depends on the incidence of *Candida* in the nursery, the gestational age of the infant, and severity of presentation (see chapter "*Candida*").

Default empiric therapy with a semisynthetic penicillin (e.g., oxacillin, nafcillin) will provide coverage against methicillin-susceptible *S. aureus*, GBS, and group A *Streptococcus*. An aminoglycoside (e.g., gentamicin, tobramycin) should be used in combination to provide coverage against most gram-negative organisms. Other antibiotics should be used in certain situations:

Vancomycin. Although CoNS is the most common cause of LOS, it is not associated with mortality or significant morbidity, and therefore empiric vancomycin can

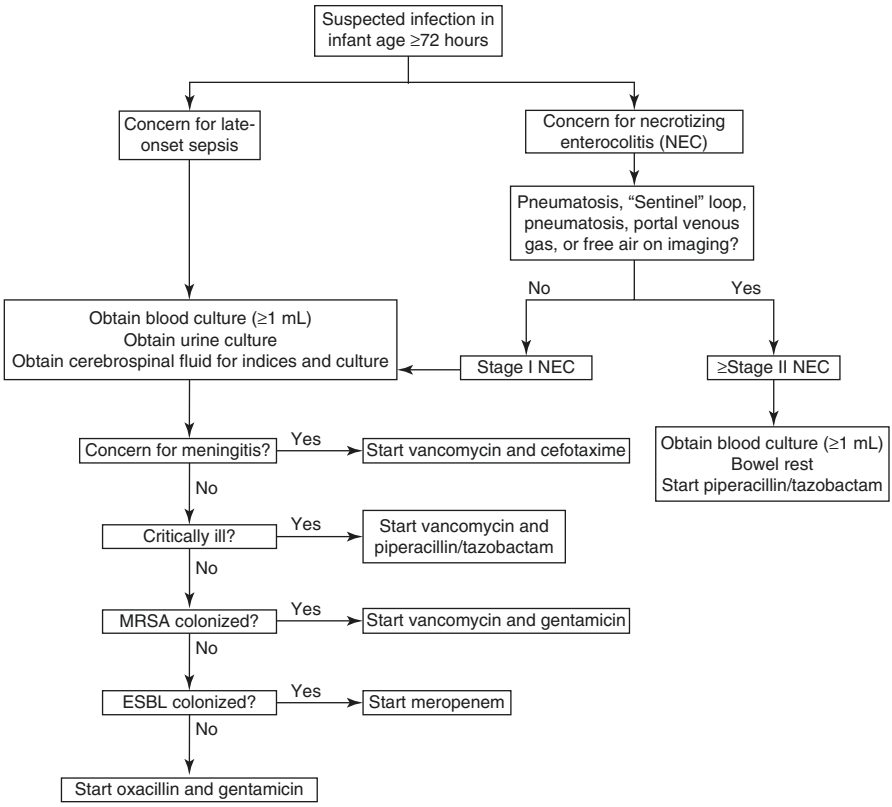

Fig. 1 Approach to suspected late-onset sepsis in the neonatal intensive care unit. For infants with suspected late-onset sepsis or stage I necrotizing enterocolitis (NEC), which has significant overlap with late-onset sepsis, cultures of blood, urine, and cerebrospinal fluid should be obtained. *Oxacillin* (or a similar semisynthetic penicillin) and *gentamicin* (or another aminoglycoside) should then be started promptly in most cases. Exceptions include (1) when meningitis is suspected based on clinical findings or cerebrospinal fluid indices (vancomycin and cefotaxime), (2) if the infant is critically ill (generally defined as new requirement for pressors, disseminated intravascular coagulation, or acute and severe respiratory failure; vancomycin and piperacillin/tazobactam), and (3) if the infant is known to be colonized with methicillin-resistant *Staphylococcus aureus* (vancomycin in lieu of oxacillin) or an extended-spectrum beta-lactamase- (ESBL) producing gram-negative organism (meropenem in lieu of oxacillin and gentamicin). Note that if NEC is confirmed (stage II or higher), then cerebrospinal fluid and urine cultures are not required and piperacillin/tazobactam should be started once blood culture is obtained

be withheld until CoNS infection is confirmed [37]. However, vancomycin should be used empirically when an infant who is known to be colonized with methicillin-resistant *S. aureus* has suspected LOS or when an infant with suspected LOS is critically ill (e.g., hypotensive, acute respiratory failure, DIC). Vancomycin should be used for definitive treatment when required, usually for CoNS (which is usually resistant to oxacillin) and methicillin-resistant *S. aureus* [38].

Cephalosporins. Third- and fourth-generation cephalosporins (e.g., cefotaxime, ceftriaxone, cefepime) are associated with increased antibiotic resistance and increased risk for *Candida* in the neonatal intensive care unit [39, 40]. Therefore, their use should be restricted to three clinical situations:

1. Treatment of suspected or proven gonococcal disease (see chapter "Neonatal Conjunctivitis")
2. Treatment of suspected or proven gram-negative meningitis
3. Treatment of early- or late-onset sepsis among infants with significant renal dysfunction for whom aminoglycosides are contraindicated

Piperacillin/tazobactam. In addition to gram-negative coverage, piperacillin/tazobactam also provides good activity against *Pseudomonas* and anaerobes. It can be used for the treatment of proven or suspected necrotizing enterocolitis (see chapter "Necrotizing Enterocolitis") or as a first- or second-line agent for critically ill infants with suspected LOS. However, it is unnecessarily broad for routine empiric use compared with aminoglycosides.

Meropenem. Carbapenems such as meropenem should be reserved for infections with extended-spectrum beta-lactamase-producing gram-negative organisms.

Definitive Therapy

If a pathogen is identified in culture, empiric therapy should be converted to definitive therapy by choosing the narrowest effective agent that will reach the infected compartment(s). Since the optimal duration of therapy has not been well established for LOS, treatment durations vary widely (Table 3). Source control is critically important in treating LOS; infected catheters or tubes should be removed whenever possible, and purulent collections should be drained.

Prevention

Since the majority of LOS episodes are associated with nosocomial transmission of and infection with pathogenic bacteria, prevention is largely centered around appropriate infection control practices. Consistent hand hygiene practices are the single most important aspect of prevention in the NICU setting [41]. Meticulous care practices during insertion and maintenance of indwelling hardware, particularly central venous catheters, can markedly reduce the risk for late-onset bacteremia (see chapter "Principles of Infection Prevention in the Nursery") [42]. Avoiding placement of catheters and removing them as soon as they are no longer needed is critical.

Other well-studied strategies include the increased use of human milk and antibiotic stewardship programs (see chapter "Antibiotic Stewardship"). There has been increasing attention paid to the use of probiotic agents for the prevention of sepsis or necrotizing enterocolitis; early studies appear promising [43].

References

1. Greenberg RG, Kandefer S, Do BT, et al. Late-onset sepsis in extremely premature infants: 2000-2011. Pediatr Infect Dis J. 2017;36:774–9.
2. Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics. 2002;110:285–91.
3. Verani JR, McGee L, Schrag SJ, et al. Prevention of perinatal group B streptococcal disease – revised guidelines from the CDC, 2010. MMWR Recomm Rep. 2010;59:1–36.
4. Gowda H, Norton R, White A, Kandasamy Y. Late-onset neonatal sepsis – a 10-year review from North Queensland, Australia. Pediatr Infect Dis J. 2017;36:883–8.
5. Cailes B, Kortsalioudaki C, Buttery J, et al. Epidemiology of UK neonatal infections: the neonIN infection surveillance network. Arch Dis Child Fetal Neonatal Ed. 2017; Available online Dec 5 2017.
6. Vergnano S, Menson E, Kennea N, et al. Neonatal infections in England: the NeonIN surveillance network. Arch Dis Child Fetal Neonatal Ed. 2011;96:F9–14.
7. Dunham EC. Septicemia in the newborn. Am J Dis Child. 1933;45:229.
8. Nyhan WL, Fousek MD. Septicemia of the newborn. Pediatrics. 1958;22:268–78.
9. Gluck L, Wood HF, Fousek MD. Septicemia of the newborn. Pediatr Clin N Am. 1966;13:1131–48.
10. Freedman RM, Ingram DL, Cross I, et al. A half century of neonatal sepsis at Yale: 1928 to 1978. Am J Dis Child. 1981;35:140–4.
11. Gladstone IM, Ehrenkranz RA, Edberg SC, et al. A ten-year review of neonatal sepsis and comparison with the previous fifty-year experience. Pediatr Infect Dis J. 1990;9:819–25.
12. Bizzarro MJ, Raskind C, Baltimore RS, et al. Seventy-five years of neonatal sepsis at Yale: 1928-2003. Pediatrics. 2005;116:595–602.
13. Pammi M, Weisman LE. Late-onset sepsis in preterm infants: update on strategies for therapy and prevention. Expert Rev Anti-Infect Ther. 2015;13:487–504.
14. Dong Y, Speer CP. Late-onset neonatal sepsis: recent developments. Arch Dis Child Fetal Neonatal Ed. 2015;100:F257–63.
15. Tarr PI, Warner BB. Gut bacteria and late-onset neonatal bloodstream infections in preterm infants. Semin Fetal Neonatal Med. 2016;21:388–93.
16. Das A, Shukla S, Rahman N, Gunzler D, Abughali N. Clinical indicators of late-onset sepsis workup in very low-birth-weight infants in the neonatal intensive care unit. Am J Perinatol. 2016;33:856–60.
17. Bekhof J, Reitsma JB, Kok JH, Van Straaten IH. Clinical signs to identify late-onset sepsis in preterm infants. Eur J Pediatr. 2013;172:501–8.
18. Okascharoen C, Hui C, Cairnie J, Morris AM, Kirpalani H. External validation of bedside prediction score for diagnosis of late-onset neonatal sepsis. J Perinatol. 2007;27:496–501.
19. Coggins SA, Weitkamp JH, Grunwald L, et al. Heart rate characteristic index monitoring for bloodstream infection in an NICU: a 3-year experience. Arch Dis Child Fetal Neonatal Ed. 2016;101:F329–32.
20. Chauhan N, Tiwari S, Jain U. Potential biomarkers for effective screening of neonatal sepsis infections: an overview. Microb Pathog. 2017;107:234–42.
21. Wu IH, Tsai MH, Lai MY, et al. Incidence, clinical features, and implications on outcomes of neonatal late-onset sepsis with concurrent infectious focus. BMC Infect Dis. 2017;17:465.
22. Fischer JE. Physicians' ability to diagnose sepsis in newborns and critically ill children. Pediatr Crit Care Med. 2005;6:S120–5.
23. Shane AL, Sanchez PJ, Stoll BJ. Neonatal sepsis. Lancet. 2017;390:1770–80.
24. Schelonka RL, Chai MK, Yoder BA, et al. Volume of blood required to detect common neonatal pathogens. J Pediatr. 1996;129:275–8.
25. Mohseny AB, van Velze V, Steggerda SJ, et al. Late-onset sepsis due to urinary tract infection in very preterm neonates is not uncommon. Eur J Pediatr. 2018;177:33–8.

26. Visser VE, Hall RT. Urine culture in the evaluation of suspected neonatal sepsis. J Pediatr. 1979;94:635–8.
27. Utsch B, Klaus G. Urinalysis in children and adolescents. Dtsch Arztebl Int. 2014;111:617–26.
28. Isaacs D, Barfield C, Clothier T, et al. Late-onset infections of infants in neonatal units. J Paediatr Child Health. 1996;32:158–61.
29. Stoll BJ, Hansen N, Fanaroff AA, et al. To tap or not to tap: high likelihood of meningitis without sepsis among very low birth weight infants. Pediatrics. 2004;113:1181–6.
30. Flidel-Rimon O, Leibovitz E, Eventov Friedman S, Juster-Reicher A, Shinwell ES. Is lumbar puncture required in every workup for suspected late-onset sepsis in neonates? Acta Paediatr. 2011;100:303–4.
31. Gibbs K, Holzman IR. Endotracheal tube: friend or foe? Bacteria, the endotracheal tube, and the impact of colonization and infection. Semin Perinatol. 2012;36:454–61.
32. Bertone SA, Fisher MC, Mortensen JE. Quantitative skin cultures at potential catheter sites in neonates. Infect Control Hosp Epidemiol. 1994;15:315–8.
33. Frederiksen B, Christiansen P, Knudsen FU. Acute osteomyelitis and septic arthritis in the neonate, risk factors and outcome. Eur J Pediatr. 1993;152:577–80.
34. Pammi M, Flores A, Leeflang M, Versalovic J. Molecular assays in the diagnosis of neonatal sepsis: a systematic review and meta-analysis. Pediatrics. 2011;128:e973–85.
35. Hedegaard SS, Wisborg K, Hvas AM. Diagnostic utility of biomarkers for neonatal sepsis – a systematic review. Infect Dis. 2015;47:117–24.
36. Bhandari V. Effective biomarkers for diagnosis of neonatal sepsis. J Pediatric Infect Dis Soc. 2014;3:234–45.
37. Cantey JB, Anderson KR, Kalagiri RR, Mallett LH. Morbidity and mortality of coagulase-negative staphylococcal sepsis in very-low-birth-weight infants. World J Pediatr. 2018; Available online Feb 25, 2018.
38. Chiu CH, Michelow IC, Cronin J, et al. Effectiveness of a guideline to reduce vancomycin use in the neonatal intensive care unit. Pediatr Infect Dis J. 2011;30:273–8.
39. de Man P, Verhoeven BA, Verbrugh HA, Vos MC, van den Anker JN. An antibiotic policy to prevent emergence of resistant bacilli. Lancet. 2000;355:973–8.
40. Cotten CM, McDonald S, Stoll B. The association of third-generation cephalosporin use and invasive candidiasis in extremely low birth-weight infants. Pediatrics. 2006;118:717–22.
41. Borghesi A, Stronati M. Strategies for the prevention of hospital-acquired infections in the neonatal intensive care unit. J Hosp Infect. 2008;68:293–300.
42. Sinha AK, Murhy V, Nath P, Morris JK, Millar M. Prevention of late onset sepsis and central-line associated blood stream infection in preterm infants. Pediatr Infect Dis J. 2016;35:401–6.
43. Dermyshi E, Wang Y, Yan C, et al. The “golden age” of probiotics: a systematic review and meta-analysis of randomized and observational studies in preterm infants. Neonatology. 2017;112:9–23.

Necrotizing Enterocolitis

Sarah Henen and Jennifer Duchon

Epidemiology

The incidence of NEC varies greatly between NICUs, with an overall incidence of approximately 5% for all infants <32 weeks gestation [1]. The incidence increases as gestational age and birth weight decrease, with an incidence of approximately 12% in infants born between 501 and 750 g, and approximately 9% in infants with a birth weight of less than 1500 g [2]. However, full-term infants comprise 10% of NEC cases [3]. There does not appear to be a differential incidence by sex, and the role of race in NEC is unclear. Outbreaks of NEC have been described, lending support to bacterial or viral agents contributing to disease.

Pathogenesis

NEC is typically described as a multifactorial disease with many predisposing elements interacting with each other in a complex manner, making the contribution of individual risk factors difficult to assess. As well, most studies evaluating risk factors are retrospective, showing associations but not causation. Most unifying theories about the etiology of NEC involve a combination of abnormal inflammatory response (both systemically and in the gut environment), colonization of intestinal mucosa by pathogenic bacteria (dysbiosis), and abnormal vascular regulation in a vulnerable host with intestinal immaturity [3].

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Prematurity is the single most consistent risk factor for NEC, with the incidence of the disease inversely proportional to gestational age [2, 4, 5]. Low birth weight, independent of gestational age, has been cited as a risk factor, implying that prenatal factors that cause growth restriction can predispose the developing gut to be vulnerable to NEC [6, 7]. Other risk factors include infants born to mothers with chorioamnionitis, preterm premature rupture of membranes, and neonatal sepsis, all of which presumably increase risk by increasing inflammation [8]. Infants who have experienced hypotension have been shown to be at higher risk of NEC, and the association between NEC and a hemodynamically significant patent ductus arteriosus has been described, with the "steal" of blood flow from the ductus implicated in vascular compromise of the preterm intestine [9, 10].

Enteral feeding practices and use of medications, specifically antibiotics and histamine-2 (H2) antagonists, are well-established targets for interventions to prevent NEC.

Enteral feeding. Most infants who get NEC have been fed; however, most infants who are fed do not develop NEC. The optimal feeding strategy for preterm infants is unknown; the optimal rate of advancement, target volume, and composition of enteral feeds in infants at risk for NEC are unclear. Many studies clearly show the protective effect of human milk**,** and this has led to the extrapolation of formula use as a risk factor for NEC [11, 12]. Most authors would cite prolonged delay in initiation of feeds and exclusive use of formula in place of breast milk as risk factors for NEC. High osmolarity of feeds via the use of bovine fortification products and rapid advancement of feeds (>30 cc/kg/day) are felt to be associated with NEC; however, the optimal osmolar threshold and timing of feeding fortification and advancement to promote growth but mitigate NEC risk are unclear.

Antibiotic use. Several observational studies have shown and increased risk of NEC or death with prolonged (typically ≥5 days) duration of antibiotics in the early neonatal period. This association is now felt to be mediated by changes in the intestinal microbiome [13, 14]. These epidemiologic studies are being confirmed with the advent of techniques that allow rapid and detailed identification of the intestinal microbial community. Through amplification and sequencing of the 16S ribosomal RNA subunit DNA or whole-genome sequencing, the contribution of the neonatal microbiome to the development of NEC has become clear. Infants with NEC have been shown to have a higher predominance of gram-negative organisms and a decreased diversity of bacteria prior to disease onset [15].

H2 Antagonists. Infants receiving H2 blockers (e.g., ranitidine, cimetidine, famotidine) have shown an increased risk of NEC. The mechanism of this association is also likely mediated in part by the alterations in the gut microbiome as well through loss of the protective effect of lowered gastric pH [16, 17].

Packed Red Blood Cell (PRBC) Transfusion. NEC temporally related to PRBC transfusion is well described and often termed transfusion-associated acute gut injury. Although the mechanism of this association is not clear, both age of blood, changes in mesenteric vascular regulation during transfusion, and degree of anemia at transfusion have been implicated [18, 19].

Full-term infants who develop NEC have a unique risk factor profile, likely because NEC in these infants is due to different underlying processes. Intestinal anomalies such as gastroschisis or Hirschsprung's disease, cyanotic congenital heart disease, maternal cocaine use, perinatal asphyxia, and growth restriction have been linked to NEC in term and near-term infants. This risk factor profile suggests perinatal or congenital conditions which result in reduced blood flow to the neonatal intestine as an important consideration in older infants who develop NEC [20, 21].

Clinical Findings

The age at presentation of NEC is inversely proportional to gestational age. In the smallest infants, the median time to onset is approximately 20 days of life, corresponding to a post-menstrual age of 28–32 weeks, when patients are typically beginning the convalescent phase of extreme prematurity [22]. Full-term or late preterm infants typically present within the first week of life, again indicating the strong contribution of perinatal insults or congenital conditions.

Clinical signs. The initial stages of NEC are comprised of non-specific signs and symptoms which overlap with other conditions such as sepsis, apnea, or feeding intolerance. Increased episodes of apnea, temperature instability, decreased activity level, oliguria, as well as intestinal signs such as feeding intolerance and abdominal distention may be present. More specific local signs include abdominal tenderness and bloody stool; abdominal wall erythema and abdominal mass are specific signs of NEC but often difficult to discern [23, 24]. Infants may rapidly progress to severe systemic signs, such as hypotension, circulatory arrest, renal failure, or respiratory failure.

Laboratory signs. Abnormal lab indices include abnormal serum glucose, hyponatremia, leukopenia, neutropenia, thrombocytopenia, and accompanying anemia. Elevated inflammatory makers are typically present. Severely affected patients will show metabolic acidosis and associated hyperkalemia as well as disseminated intravascular coagulopathy (DIC) [25]. Elevated eosinophil count, when present, may be specific for NEC.

Radiographic signs. Pneumatosis intestinalis, or the projection of gas in the bowel wall as seen on X-ray, is the pathognomonic finding of NEC. Portal venous gas, which is an extension of this intraluminal air into the portal venous system, is also classic radiographic criterion of NEC. Infants who progress to intestinal perforation may display free intraperitoneal air on radiographs; this can be illustrated by the "football sign," an illumination of the falciform ligament by free intra-abdominal air. Other, less specific findings of NEC that may overlap with other conditions are fixed and/or dilated intestinal loops of bowel, bowel wall edema, and/or stacked loops of bowel with or without air fluid levels [23, 26]. Figure 1 shows radiographic examples of pneumatosis, portal venous gas, and perforation.

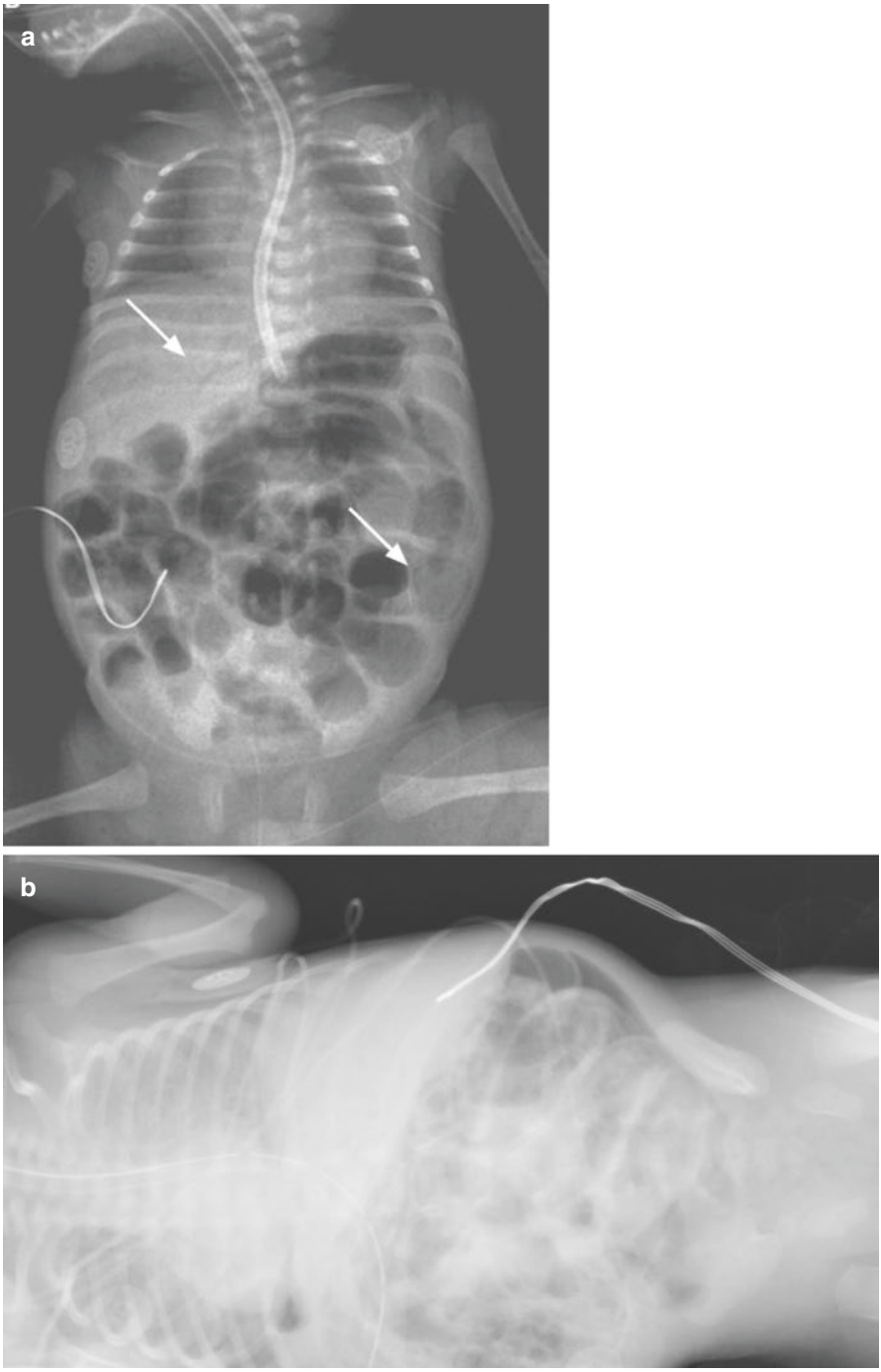

Fig. 1 Radiographic findings of necrotizing enterocolitis. (**a**) Pneumatosis intestinalis (lower arrow) and portal venous gas (upper arrow); (**b**) free intraperitoneal air as seen on a decubitus radiograph. Used with permission from [23]

Diagnosis

The diagnosis of NEC is based on a combination of clinical, radiological, and lab findings as mentioned above. Historically, the most common clinical staging system is the modified Bell's staging (Table 1), which categorizes NEC into Stages I, II, and III (i.e., suspected, definite, and advanced/surgical) [27–29]. The Centers for Disease Control and Prevention National Healthcare Safety Network (NHSN) has also developed diagnostic criteria for NEC, which is categorized as a healthcare-acquired infection [30]. These overlap with the Vermont Oxford Network definition of NEC, which is widely used for quality assurance and research purposes among nurseries [31].

Table 1 Modified Bell's staging for necrotizing enterocolitis (NEC)

Stage	Classification of NEC	Systemic signs	Abdominal signs	Radiographic signs	Treatment
IA	Suspected	Temperature instability, apnea, bradycardia, lethargy	Gastric residuals, abdominal distention, emesis, occult blood in stool	Normal or intestinal dilation, mild ileus	NPO, antibiotics for 3 days, pending cultures and stomach decompression
IB	Suspected	Same as IA	Grossly bloody stool	Same as above	Same as IA
IIA	Definite, mildly ill	Same as IA	Same as above; plus absent bowel sounds, +/− abdominal tenderness	Intestinal dilation, ileus, pneumatosis intestinalis	Same as IA; NPO and antibiotics for 7–10 days
IIB	Definite, moderately ill	Same as IA, plus mild metabolic acidosis and thrombocytopenia	Same as above; absent bowel sounds, definite tenderness, +/− abdominal cellulitis or mass	Same as IIA, +/− ascites, +/− portal venous gas	Same as IIA, NPO and antibiotics for 14 days
IIIA	Advanced, severely ill, intact bowel	Same as above, plus hypotension, bradycardia, apnea, severe acidosis, DIC, and neutropenia	Same as above, plus signs of peritonitis, marked tenderness, and abdominal distention	Same as IIA, plus definite ascites	Same as IIB plus volume replacement, inotropic and ventilator support. If no improvement, consider surgical intervention
IIIB	Advanced, severely ill, perforated bowel	Same as IIIA	Same as IIIA	Same as IIIA, plus pneumoperitoneum	Same as IIIA plus surgical intervention

DIC disseminated intravascular coagulation. Adapted from 26–28

These classification systems are often used as a diagnostic tool, although Bell criteria are meant to be applied to infants already diagnosed with NEC. Abdominal radiographs in preterm neonates may be difficult to evaluate, and diagnosis of radiographic findings such as pneumatosis intestinalis may vary from reader to reader [26, 32, 33]. Some infants with severe disease requiring surgical management never develop pneumatosis or portal venous gas. Additionally, NEC in very preterm infants may not present with bloody stools. In this population, intestinal necrosis develops proximal to the ileocecal valve; when ileus is present, blood will fail to pass into the distal part of the colon. Pneumoperitoneum on radiographs may or may not be associated with intestinal necrosis; spontaneous intestinal perforation – an entity which is clinically and pathologically distinct from NEC – often presents as free air in the abdominal cavity. Table 2 highlights the differences between SIP and NEC. Rarely, dissected air from the pleural cavity in infants with severe lung disease or pneumothorax may present with pneumoperitoneum [34, 35]. Ultrasonography may detect bowel wall edema, pneumatosis, alterations in the intestinal vascular state, ascites, or intra-abdominal collections in infants with NEC. This technique provides specificity of diagnosis but requires both operator skill and an experience in interpretation [36, 37].

As discussed, many laboratory abnormalities occur with NEC, and inflammatory markers are usually quite elevated. However, specific serum, urine, or stool biomarkers have not yet been validated. Intestinal fatty acid-binding protein, a protein present in enterocytes and released with cell injury; fecal calprotectin, released from neutrophils during an inflammatory response; and serum amyloid A and IL-8,

Table 2 Clinical features of spontaneous intestinal perforation versus necrotizing enterocolitis

	Spontaneous intestinal perforation	Necrotizing enterocolitis
Onset	Age < 10 days	Age > 14 days
Abdominal signs		
Distention	+++	+++
Erythema	–	+
Tenderness	+/–	+++
Bilious aspirates	++/–	++
Laboratory markers		
Leukopenia/neutropenia	–	+++
Thrombocytopenia	–	+++
DIC	–	++
Physiologic signs		
Apnea	+/–	++
Temperature Instability	–	++
Hypoperfusion/shock	–	+++
Radiographic signs		
Pneumatosis intestinalis	–	+++/–
Hepatobiliary gas	–	++/–
Pneumoperitoneum	+++	++/–

DIC disseminated intravascular coagulation