JOHNS HOPKINS ALL CHILDREN'S HOSPITAL

Early-Onset Sepsis in the Neonatal Intensive Care Unit Clinical Pathway

JOHNS HOPKINS
All Children's Hospital

Johns Hopkins All Children's Hospital

Early-Onset Sepsis in the Neonatal Intensive Care Unit Clinical Pathway

Table of Contents:

Primary Author: Noura Nickel, MD

Updated: April 30, 2026

Johns Hopkins All Children's Hospital

Early-Onset Sepsis in the Neonatal Intensive Care Unit Clinical Pathway

Rationale:

This clinical pathway was developed by a consensus group of Johns Hopkins All Children's Hospital (JHACH) physicians, advanced practice providers, nurses, and pharmacists to standardize the management of neonates hospitalized in the Neonatal Intensive Care Unit (NICU) being evaluated and treated for early-onset sepsis (EOS).

This pathway offers a general understanding of EOS, an evidence-based approach to its evaluation, and guidance for the appropriate type and duration of antimicrobial therapy based on the final diagnosis.

The American Academy of Pediatrics (APP) Committee on the Fetus and Newborn has published EOS management guidelines, which help guide clinicians in determining the appropriate approach for risk assessment and screening for EOS in neonates born ≥ 35 weeks' gestational age (GA).[1]

This clinical pathway will focus on the evaluation and management of neonates admitted to the NICU, assuming they are being evaluated for EOS, as this population has certain risk factors or clinical illness that warrant further EOS evaluation.

Background:

Definitions:
EOS, defined as culture-positive infection usually in the first 3 days of life, is a common diagnosis in the newborn population associated with increased risk of morbidity and mortality. Although the exact timing of differentiating EOS from late-onset sepsis (LOS) may not be clear, EOS differs from LOS based on the most likely causative pathogens, where EOS pathogens are transmitted perinatally and LOS pathogens are acquired postnatally. Premature neonates, and particularly those admitted to the NICU, are more likely to be diagnosed with EOS due to risk factors associated with their underlying conditions, presence of central lines, endotracheal tubes, need for parenteral nutrition, and other risk factors.

Incidence:
EOS has decreased over the years in response to successful efforts to administer intrapartum antibiotic prophylaxis (IAP) to mothers with prespecified risk factors.[2] In the United States, the rates of EOS are 0.8 – 1.1 per 1,000 live births. However, premature neonates are at increased risk for EOS, with an incidence of 13.9 cases per 1,000 live births for those between 22 – 28 weeks' GA[3], and up to 45.4 cases per 1,000 live births in those ≤ 23 weeks' GA.[4]

Microbiology:
Pathogens responsible for EOS often ascend from the genitourinary tract of a pregnant mother, although transplacental blood-borne transmission can also occur. The most common causative pathogens for EOS are Group B *Streptococcus* (GBS) and *Escherichia coli* (EC), accounting for two-thirds of EOS infections in neonates. Despite IAP for GBS prevention, it remains the most common cause of EOS in term neonates, while EC is the most common cause of EOS in preterm neonates.[3] Additional less common causative pathogens include *Staphylococcus aureus*, *Enterococcus* species, other *Streptococcus* species, *Listeria monocytogenes*, *Haemophilus* species, *Klebsiella* species; as well as fungal etiologies, including *Candida* species.[3-5]

Extremely premature neonates are frequently delivered secondary to concern for intraamniotic infection and are at increased risk for morbidity and mortality related to infectious disease. The incidence of EOS in less than 28 weeks' GA is significantly higher than in other preterm neonates, and for the previable neonates between 22 – 24 weeks' GA, the risk is highest. Specifically, the risk of EOS due to EC is rising over time, and the incidence of ampicillin-resistant EC is also increasing.[5]

Risk factors:
Well-established risk factors for EOS include GBS colonization, prolonged rupture of membranes (PROM) (> 18 hours), maternal intrapartum fever or fetal tachycardia as a sign of potential maternal intraamniotic infection, and preterm labor. Additional risk factors include mothers who are experiencing disadvantages associated with low socioeconomic status, poverty, food insecurity, substance use, and limited prenatal care. Some obstetric practices that may increase the risk of EOS include membrane sweeping, cervical examinations, fetal scalp monitoring, and instrumented vaginal delivery.

The strongest predictors of EOS are GA, presence of intraamniotic infection, and neonatal clinical illness. As preterm labor and PROM can often be in the setting of an intraamniotic infection, preterm neonates are empirically evaluated for EOS in up to 80% of cases, despite the incidence of true EOS being much lower.[6]

Clinical presentation:
Clinical signs and symptoms of neonatal sepsis can be broad, non-specific, and overlap with other common early-presenting neonatal pathologies, including respiratory distress syndrome, meconium aspiration syndrome, perinatal asphyxia, adrenal insufficiency, and many others. No specific clinical characteristic has been identified to be significantly associated with EOS.[5]

Outcomes:
EOS is associated with an increased risk of morbidity and mortality. Factors that impact these outcomes include GA, where the more premature neonates have a higher risk of mortality. There are also pathogen-specific differences in mortality, with the highest rates among those infected with gram-negative bacteria and fungal pathogens.[3,4] Among neonates who survive,

there is an increased risk of chronic morbidities, including retinopathy of prematurity, neurodevelopmental impairment, and bronchopulmonary dysplasia.[4,7]

Diagnosis:

Evaluation:
The standard diagnostic for EOS is obtaining at least 1 mL of blood for culture before initiating antimicrobials. This volume is effective in detecting low-level bacteremia and fungemia of common neonatal pathogens.[8] Larger blood volumes, or additional blood cultures, can be obtained to increase the positivity yield and decrease the likelihood of false-negative culture results. Cerebrospinal fluid (CSF) cultures should be obtained for neonates at high risk of EOS based on risk factors and clinical illness severity.[9,10]

Lumbar punctures (LP) to evaluate for congenital meningitis are inconsistently performed. In a study evaluating the incidence of EOS in over 217,000 live births, 235 cases had EOS, with 165 having an LP performed.[5] From this, only 6 cases of early-onset meningitis were detected.[5] Additionally, CSF cultures were all obtained after initiation of antimicrobial therapy, with a median difference of 1 day between blood and CSF cultures.[5]

Antimicrobial exposure without true infection increases the risk of certain complications, such as necrotizing enterocolitis (NEC), antimicrobial resistance, and risk of later infection. There are efforts to minimize the exposure of lower-risk premature neonates to unnecessary antimicrobial exposure. Efforts to do this have demonstrated safety in withholding of EOS evaluation and prolonged antimicrobial use (≥ 5 days) in “low risk” premature neonates 22 – 28 weeks’ GA, which include neonates born via c-section, rupture of membranes at the time of delivery, and no concern for clinical intrauterine infection.[11]

It is not recommended to obtain inflammatory biomarkers such as C-reactive protein (CRP) or procalcitonin for evaluation of EOS due to the impact that other non-infectious pathologies can have on abnormal levels of these biomarkers.[12] Certain components of the complete blood count (CBC), specifically the presence of leukopenia, neutropenia, and an elevated immature to total neutrophil ratio, can be associated with culture-positive infection. There are low sensitivities associated with these cutoff values, and they should not be used as the sole purpose of ruling in or out EOS.[13]

Clinical Management:

Antimicrobial therapy:
The AAP continues to recommend the use of intravenous (IV) ampicillin and gentamicin for empiric coverage in EOS in both term and preterm neonates.[9,10] However, concerns are emerging about antimicrobial-resistant organisms, specifically ampicillin-resistant EC, as well as the emergence of aminoglycoside-resistant EC. Because of this, there is a recommendation to broaden antibiotic coverage in ill-appearing high-risk neonates, which includes those born to mothers with PROM, mothers with exposure to beta-lactams, and when there is concern for

intraamniotic infection.[9,10] In a study evaluating the incidence of EOS in neonates, 74.1% of EC isolates were found to be resistant to ampicillin, with the highest incidence in mothers who had received ampicillin for IAP.[5] Furthermore, 7% of isolates were resistant to both ampicillin and gentamicin.[5] These resistance patterns were higher in preterm compared to term neonates.[5]

Duration of antimicrobial therapy (diagnosis-based recommendations):

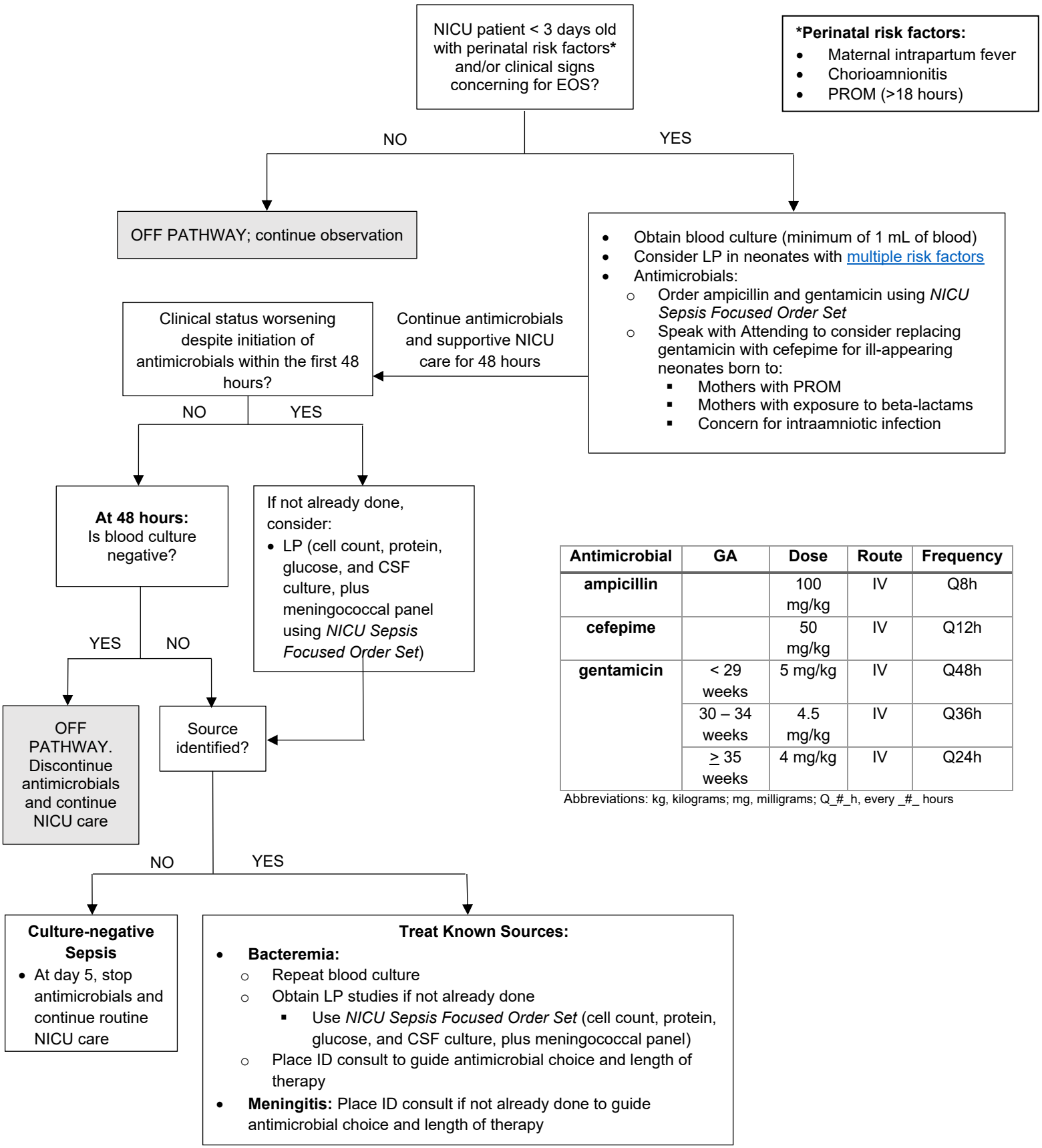
Sepsis rule-out: For neonates with a negative blood culture at 48 hours, the recommendation is to discontinue antimicrobials. This assumes the culture volume was at least 1 mL of blood obtained before initiation of antimicrobials in the neonate.

Culture-negative sepsis: The diagnosis of “culture-negative sepsis” (CNS) is often made when a neonate is treated with a course of antimicrobials in the absence of a positive blood culture. Clinicians will often treat neonates for CNS in the context of EOS because the clinical presentation of sepsis in neonates is frequently nonspecific, and the consequences of missing a true infection can be catastrophic. CNS accounts for most of the antimicrobial exposure in the first postnatal week, with CNS being far more frequent than culture-proven EOS and contributing disproportionately to overall antimicrobial days, despite low associated mortality and significant diagnostic uncertainty.[14,15] If a clinician strongly believes a neonate has a bacterial infection despite a negative blood culture, the recommended course of treatment for CNS should be limited to 5 days.

Culture-confirmed sepsis (bacteremia or meningitis): The duration of antimicrobial therapy depends on various factors, including the identified pathogen, time to clearance, and source of infection. Consultation with Infectious Diseases (ID) is recommended to determine the length of antimicrobial therapy.

Johns Hopkins All Children's Hospital

NICU Early-Onset Sepsis Clinical Pathway



Antimicrobial	GA	Dose	Route	Frequency
ampicillin		100 mg/kg	IV	Q8h
cefepime		50 mg/kg	IV	Q12h
gentamicin	< 29 weeks	5 mg/kg	IV	Q48h
	30 – 34 weeks	4.5 mg/kg	IV	Q36h
	≥ 35 weeks	4 mg/kg	IV	Q24h

Abbreviations: kg, kilograms; mg, milligrams; Q_#_h, every _#_ hours

References:

1. Dhudasia MB, Flannery DD, Pfeifer MR, Puopolo KM. Updated guidance: Prevention and management of perinatal group B streptococcus infection. *NeoReviews*. 2021;22(3).
2. ACOG. Prevention of group B streptococcal early-onset disease in newborns. *Obstetrics & Gynecology*. 2020;135(2):e51–e72.
3. Stoll BJ, Puopolo KM, Hansen NI, et al. Early-onset neonatal sepsis 2015 to 2017, the rise of Escherichia coli, and the need for novel prevention strategies. *JAMA Pediatr*. 2020;174(7).
4. Flannery DD, Edwards EM, Puopolo KM, Horbar JD. Early-onset sepsis among very preterm infants. *Pediatrics*. 2021;148(4).
5. Stoll BJ, Puopolo KM, Hansen NI, et al. Early-onset neonatal sepsis 2015 to 2017, the rise of Escherichia coli, and the need for novel prevention strategies. *JAMA Pediatr*. 2020;174(7).
6. Flannery DD, Ross RK, Mukhopadhyay S, Tribble AC, Puopolo KM, Gerber JS. Temporal trends and center variation in early antibiotic use among premature infants. *JAMA Netw Open*. 2018;1(1).
7. Mukhopadhyay S, Puopolo KM, Hansen NI, et al. Impact of early-onset sepsis and antibiotic use on death or survival with neurodevelopmental impairment at 2 years of age among extremely preterm infants. *J Pediatr*. 2020;221:39–46.e5.
8. Capt RL, Schelonka U, Mc, et al. Volume of blood required to detect common neonatal pathogens. *The Journal of Pediatrics*. 1996;129(2).
9. Puopolo KM, Benitz WE, Zaoutis TE. Management of neonates born at ≤34 6/7 weeks' gestation with suspected or proven early-onset bacterial sepsis. *Pediatrics*. 2018 Dec;142(6):e20182896.
10. Puopolo KM, Benitz WE, Zaoutis TE. Management of neonates born at ≥35 0/7 weeks' gestation with suspected or proven early-onset bacterial sepsis. *Pediatrics*. 2018 Dec;142(6):e20182894.
11. Puopolo KM, Mukhopadhyay S, Hansen NI, et al. Identification of extremely premature infants at low risk for early-onset sepsis. *Pediatrics*. 2017 Nov;140(5):e20170925.
12. Tiozzo C, Mukhopadhyay S. Noninfectious influencers of early-onset sepsis biomarkers. *Pediatr Res*. 2021;91(2):425
13. Hornik CP, Benjamin DK, Becker KC, et al. Use of the complete blood cell count in early-onset neonatal sepsis. *Pediatric Infectious Disease Journal*. 2012;31(8):799.
14. Dimopoulou V, Klingenberg C, Navér L, et al. Antibiotic exposure for culture-negative early-onset sepsis in late-preterm and term newborns: An international study. *Pediatr Res*. 2024;97(5):1629.
15. Flannery DD, Green MB. Antibiotics for culture-negative neonatal early-onset sepsis: Measuring the unmeasurable. *Pediatr Res*. 2024;97(5):1443.
16. Nissen MD. Congenital and neonatal pneumonia. *Paediatric Respiratory Reviews*. 2007;8(3):195.
17. Cantey JB, Wozniak PS, Pruszynski JE, Sánchez PJ. Reducing unnecessary antibiotic use in the neonatal intensive care unit (SCOUT): A prospective interrupted time-series study. *The Lancet Infectious Diseases*. 2016;16(10):1178.

Outcome Measures:

- Providers appropriately defining infection type
- Based on diagnosis, treat with appropriate/recommended antimicrobials
- Treating for an appropriate duration of time

Clinical Pathway Team

Early-Onset Sepsis in the Neonatal Intensive Care Unit Clinical Pathway

Johns Hopkins All Children's Hospital

Owner: Noura Nickel, MD

Pathway Review Panel: Fernando Bula, MD; Katie Namtu, PharmD; Tifani Russel, DNP; Sarah Tonkin, RN; Meghan Rooney, RN

Clinical Pathway Management Team: Courtney Titus, PA-C, Director; Kristel Lassiter, APRN, Implementation Specialist

Date Approved by MFNI Clinical Practice Council: October 9, 2025

Date Approved by Clinical Pathway Development Committee: November 4, 2025

Date Approved by JHACH Clinical Practice Council: N/A

Content Last Revised: November 6, 2025

Date Available on Webpage: April 30, 2026

Disclaimer: