Newborn Critical Care Center (NCCC) Clinical Guidelines

Evaluation and Management of Sepsis in the First Week After Birth

BACKGROUND

Early-onset sepsis (EOS) is defined as culture-confirmed bacterial infection of the blood and/or cerebrospinal fluid (CSF) within 72 hours after birth. The incidence of EOS increases with prematurity with 0.5 cases per 1000 infants born ≥37 weeks' gestation, 1 case per 1000 infants born at 34 to 36 weeks' gestation, 6 cases per 1000 infants born at <34 weeks' gestation, 20 cases per 1000 infants born at <29 weeks' gestation, and 32 cases per 1000 infants born at 22 to 24 weeks' gestation.[1]

Although *GBS* has been the most common pathogen in term neonates for several decades, *E. coli* is rapidly overtaking *GBS* as the number one cause for EOS. *E. coli* is the most common pathogen in preterm EOS (51%), and data from the NRN cohort (2015-2017) suggest that *E. coli* is more common than *GBS* in all infants combined (37% vs. 30%).[2] *Haemophilus* species and *Staphylococcus aureus* isolates are the third and fourth most isolated species in VLBW infants, respectively, whereas *Enterococcus* and *viridans* group streptococci are the third and fourth most isolated species in term infants. Other pathogens in both preterm and term infants include *group A streptococci* and other enteric gram-negative organisms, including *Klebsiella*, *Enterobacter, Citrobacter, Acinetobacter, and Pseudomonas. Listeria monocytogenes*, once ranked as the third most common pathogen in EOS, is not commonly implicated in any of the recent cohort studies.

This guideline addresses evaluation and management of sepsis in the first week after birth, with a focus on EOS.

EVALUATION OF EOS

Evaluation of EOS in neonates ≥35 weeks

When evaluating EOS in the first 24 hours after birth in neonates at least 35 weeks' gestation, the Kaiser EOS calculator should be used to guide clinical decisions. The Kaiser Permanente sepsis calculator is a multivariate predictive model that combines objective data available at the time of birth with clinical exam findings to estimate EOS risk and guide clinical decision making (https://neonatalsepsiscalculator.kaiserpermanente.org/).[3,4] A meta-analysis of six high-quality non-randomized controlled trials conducted in 2017 or later found a statistically significant decrease in early antibiotic use in neonates for which the sepsis calculator was used when compared to the standard approach recommended by the CDC.[5] In 2018, the AAP endorsed the calculator as one approach to evaluate the risk of EOS in neonates at birth.[6]

When using the calculator, clinicians should select the CDC national rate for EOS of 0.5/1000 live births as the baseline incidence to determine probability. The results of the sepsis calculator can be useful to support clinical decisions but are not intended to be a substitute for clinical judgement.

Evaluation of EOS in neonates < 35 weeks

Neonates <35 weeks born to a mother with any of the following risk factors are considered high-risk for EOS and should undergo a sepsis evaluation:

- Preterm rupture of membranes (ROM) and/or prolonged ROM (i.e., >18 hours)
- Preterm onset of labor
- Confirmed diagnosis of intra-amniotic infection
- Suspected intra-amniotic infection (maternal fever ≥ 39 degrees C or a temperature 38-38.9 degrees C for more than 30 minutes plus one or more of the following: maternal leukocytosis, purulent cervical drainage, and fetal tachycardia).

Neonates <35 weeks born for maternal indications (e.g., maternal pre-eclampsia) or born via Cesarean section with ROM at delivery and no concern for chorioamnionitis are considered low-risk for EOS. These low-risk neonates need not undergo immediate sepsis evaluation but instead may be monitored clinically; if the neonate has respiratory and/or cardiovascular instability after birth, sepsis evaluation may be warranted.[1]

Components of an evaluation for sepsis in the first week after birth

Blood culture is the diagnostic standard for evaluation of sepsis. The median time to positivity of neonatal blood cultures is 21.33 hours (Q1-Q3 13.17-32.46; n=437 positive blood cultures).[7]

Urine culture is not indicated in sepsis evaluations performed at <72 hours after birth.

If a neonate exhibits clinical signs of meningitis in the first week after birth, a lumbar puncture to obtain CSF for culture should be performed, and ideally prior to initiation of empiric antibiotics. However, lumbar puncture should not be performed if the neonate's clinical condition would be compromised by the procedure, and initiation of antibiotic therapy should not be delayed by the procedure. If blood cultures grow a pathogen, a lumbar puncture to obtain CSF for culture and analysis should be performed (provided the neonate's clinical condition will tolerate it) to optimize the type and duration of antibiotic therapy.

While CBCs are typically performed with blood cultures, the clinical utility of a CBC to evaluate for sepsis is low. No CBC-derived index is sensitive enough to reliably rule out EOS in neonates, thus CBCs should not be used as a proxy for obtaining a blood culture when there is concern for sepsis. Low WBC count, low absolute neutrophil count, and high immature-to-total neutrophil ratio are associated with increasing odds of infection.[8] However, fetal bone marrow depression secondary to maternal preeclampsia or placental insufficiency may result in similarly abnormal values that are not attributable to infection. Additionally, WBC and ANC increase rapidly in the first six hours after birth and level off thereafter.[9] Given this physiologic increase, the usefulness of a CBC in distinguishing between neonates with and without infection increases during the first hours after birth.[8] When interpreting CBC results, the timing of the sample should be considered.

EMPIRIC ANTIBIOTIC THERAPY

The clinical decision to initiate empiric antibiotic coverage in neonates being evaluated for sepsis is made on an individual basis and is guided by the neonate's clinical status and evaluation of the presence of risk factors for sepsis.

Empiric antibiotic coverage is aimed at providing broad-spectrum coverage for the organisms most commonly implicated in sepsis in the first week after birth. Combination therapy with a beta lactam (ampicillin) and aminoglycoside (gentamicin) is most commonly used. Standard dosing (rather than meningitic dosing) should be used as the default for empiric antibiotic coverage.

For infants with renal impairment or suspected CNS involvement, an alternative combination therapy of ampicillin and a cephalosporin (cefepime or cefotaxime) should be considered.[10] If there is high clinical suspicion for CNS involvement, meningitic dosing for ampicillin and cefepime should be used per Neofax recommendations.

When empiric antibiotic coverage is initiated due to concern for sepsis in the first week after birth, it should be discontinued after 36 hours if blood cultures are negative and the neonate is clinically stable.[4,11]

TARGETED ANTIBIOTIC THERAPY FOR CULTURE-PROVEN SEPSIS

Culture-proven infection with *Staphylococcus aureus* warrants an Infectious Disease consult; consultation may be considered for other culture-proven infections. Targeted antibiotic coverage is determined on the basis of the UNC Antibiogram and the neonate's clinical status until organism sensitivities have resulted.

The necessity/timing of serum drug concentration monitoring is driven by duration of treatment, gestational age, and clinical status. A plan for serum drug concentration monitoring should be determined in conjunction with a pharmacist.

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