Clinical Performance Guideline
Neonatal Resource Services
Early-Onset Neonatal Sepsis

Medical Necessity Guideline

Purpose: To provide guidelines to determine the optimal course of treatment and subsequent case management of early-onset neonatal sepsis (EONS).

Target Client Population: This guideline applies to term and preterm neonates that have clinical evidence of suspected or confirmed early-onset sepsis with a planned treatment course of antibiotics. Symptoms of neonatal sepsis may be non-specific but are rarely subtle.

Background	Neonatal sepsis, an infection in the bloodstream with systemic response, remains a major cause of mortality and morbidity in both term and preterm infants in the first month of life. It may be categorized as early-onset (EOS), occurring ≤ 72 hours, or late onset (LOS), occurring after 72 hours of age up to the first week of life. Early onset infection may be acquired in utero through the transplacental or transcervical route, during delivery or after birth. Symptoms of neonatal sepsis may include disturbances/alterations in feeding, respirations, cardiovascular status, temperature, activity or urination. Risk factors for EOS include maternal GBS colonization (especially if not treated during labor), prematurity, prolonged rupture of membranes, preterm rupture of membranes, chorioamnionitis consisting of intrauterine inflammation, infection or both, and maternal urinary tract infection. The primary pathogens causing early-onset neonatal sepsis in the United States are group B streptococcus (GBS) and Escherichia coli (E. coli). Obstetrical implementation of universal maternal screening for GBS with intrapartum antibiotic prophylaxis has reduced the incidence of early onset neonatal GBS sepsis from 1.8 in the early 1990's to 0.25/1,000 live births in 2010. (Oh, 2013; Bizzarro, 2015) There are few reliable laboratory tools, besides blood culture, to assist in confirming EOS. Therefore, repeated clinical examination over time may identify those truly symptomatic infants from those exhibiting transitional symptoms that improve over the first few hours of life. Significant variation in antibiotic use persists between units and is not driven by differences in the patient population. Efforts in individual units should be focused around enhanced stewardship, including the judicious use of antibiotics, avoiding unwarranted administration and the timely discontinuation when indicated. (Schulman, 2015) An undesired impact of early onset sepsis evaluation includes separation of the mother/infant dyad and decreased breastfeeding rates. (Mukhopadhyay, 2015)

Treatment Criteria	Clinical evidence in the medical literature supports the following:
	• Newborns who exhibit signs of early-onset sepsis should have the following evaluation performed:
	  ○ Blood culture
	  ○ CBC with WBC differential and platelet count
	  ○ Lumbar puncture if clinically indicated (e.g., positive blood culture, neurologic symptoms, failure to demonstrate clinical improvement)
	  ○ Chest x-ray if the infant is presenting with altered respiratory status

	• Newborns who exhibit signs of early-onset sepsis should have antibiotic therapy initiated with broad-spectrum agents such as ampicillin and an aminoglycoside until the causative pathogen is identified. Antimicrobial treatment should be narrowed to the specific pathogen(s) based on culture and sensitivity results.
	• Asymptomatic infants <37 weeks' gestation with risk factors (rupture of membranes ≥18 hours without antepartum prophylaxis) should have the following evaluation and treatment performed:
	  ○ Blood culture at birth
	  ○ CBC with differential and platelets at birth and/or 6-12 hours
	  ○ If signs of sepsis develop, a complete evaluation and antibiotic therapy can be initiated with broad-spectrum agents effective against pathogens which cause neonatal sepsis. Antibiotic therapy should be discontinued once blood culture results are known. An incubation period as short as 36 hours is sufficient to detect a pathogenic organism from a blood culture. (Lefebvre, 2015) Persistently abnormal laboratory data (CBC and/or CRP) may justify a longer treatment course. (Polin, 2012) Any abnormal CBC result obtained following birth should be corroborated at 6-12 hours of age to substantiate antibiotic treatment beyond 48 hours of life in an asymptomatic infant. (CDC, 2010)
	• There is a lack of data to support antibiotic treatment beyond 48 hours in an asymptomatic infant born to a woman with chorioamnionitis when the blood culture is negative and CBC/CRP is normal.
	• Placenta examination leading to a diagnosis of histologic chorioamnionitis does not contribute to the diagnosis of early onset sepsis in term infants. (Cuna, 2014)
	• Asymptomatic term infants of GBS colonized mothers' > 37 weeks gestation with ruptured membranes < 18 hours without adequate maternal GBS prophylactic antibiotics should receive hospital observation for ≥ 48 hours (CDC, 2010)
	• Antibiotic treatment for group B streptococci bacteremia without a defined focus should be administered for 10 days. For treatment of uncomplicated GBS meningitis, at least 14 days of antibiotic therapy should be administered. Gram-negative meningitis should be treated for either a minimum of 21 days or 14 days after a negative CSF culture. (Polin, 2012)
	• Inability to obtain CSF for analysis should prompt consideration for ultrasound-assisted guidance to support antibiotic therapy duration when repeated attempts have failed. (Peterson, 2005) This is particularly important if antibiotic therapy will be extended due to lack of CSF for analysis.
	• Antimicrobial therapy should be discontinued at 48 hours if blood culture results are negative and the likelihood of sepsis is low. (Ho, 2015) Abnormal CBC and/or CRP in an asymptomatic infant in the absence of maternal chorioamnionitis do not support antimicrobial therapy beyond 48 hours. (Polin, 2012; Benitz, 2015)
	• In infants treated for clinical suspicion of sepsis or due to maternal chorioamnionitis with negative blood culture at 48 hours, serial normal CBC and/or CRP tests are highly predictive of the absence of infection and should

	be relied upon to stop antibiotic exposure. (Benitz, 2015) • Antibiotics may be continued for more than 48 hours if there is a positive blood/CSF culture, pneumonia or a high index of suspicion for presumed clinical sepsis. ○ Chest x-ray and symptoms that resolve within 24 hours is not typical for pneumonia. • Newer screening algorithms have the potential to minimize unnecessary screening tests and/or treatment while supporting adequate monitoring in the interim. (Escobar, 2014) Since the release of the 2010 CDC recommendations newer techniques for EONS assessment have evolved with more recent interest in tools such as the risk calculator: https://neonatalsepsiscalculator.kaiserpermanente.org/ (Kuzniewicz, 2017) • There are many ways to manage asymptomatic infants with emphasis on observation in lieu of treatment. Each infant requires individualized observation. • Intravenous immune globulin has not been shown to be efficacious on the outcomes of neonatal sepsis. (INIS Collaborative Group, 2011) (Please refer to Appendix A for a detailed algorithm from the CDC, 2010)
Clinical Evidence	• A cohort study by Kuzniewicz et al (2017) evaluated the use of neonatal EOS risk prediction models on the utilization of antibiotics and extent of sepsis evaluations in infants ≥ 35 weeks' gestation. The total number of infants included in this study was 204,485 and investigations included three periods of EOS management: 1) 1/1/2010-12/31/2012 based on national recommendations in guidelines, 2) 12/1/2012-6/30/2014 using multivariable estimates of sepsis risk at birth, and 3) 7/1/2014-12/31/2015 using the EOS calculator. Utilization of the EOS calculator decreased the use of blood cultures from 14.5% (baseline period) to 4.9% and antibiotic administration in the first 24 hours of life from 5.0% to 2.6%. The number of infants with culture-confirmed EOS and the incidence of adverse clinical outcomes in the three time periods were similar. The authors concluded that utilization of risk prediction models decreased the number of infants receiving empirical antibiotics and undergoing sepsis evaluations without increasing the number of adverse outcomes. • A retrospective cohort study by Oliver et al (2016) utilized data from the Pediatric Health Information System to evaluate the use of empiric antibiotics for EONS in the United States. Information that was evaluated included the frequency of antibiotic initiation within three days of birth, the duration of the first course of antibiotics and the variation among the hospitals reporting. The records of 158,907 infants discharged from NICUs were analyzed and demonstrated that 118,624 (74.7%) infants had received antibiotics on or before postnatal day 3. Marked interhospital variation was identified in regards to the proportion of infants that had received antibiotic therapy in addition to the number of treatment days. The authors concluded that overtreatment of infants utilizing antibiotic therapy for culture unconfirmed EONS is both common and costly. • Berardi et al (2016) performed a retrospective cohort study to evaluate the use of serial physical examinations (SPE) for managing infants at-risk for EOS.

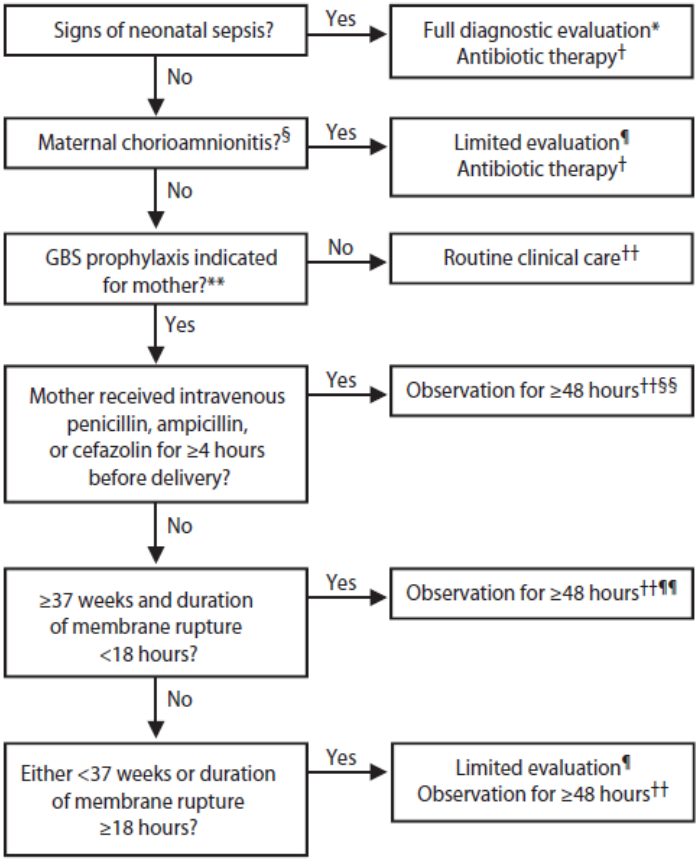
	Review of 2,092 neonatal records of live births included one culture-proven EOS. The infants managed utilizing the SPE strategy (n=216) all had normal outcomes with 12 undergoing subsequent sepsis workup and four administered empirical antibiotics. The authors concluded that the SPE strategy reduced unnecessary laboratory evaluations and antibiotics without increasing adverse outcomes in neonates who are at-risk for EOS. • A retrospective study by Lefebvre et al (2015) reviewed positive blood cultures obtained from infants over a 5-year time period and calculated the time to positivity. The collection of 3,559 blood cultures demonstrated that an incubation period of 36 hours was sufficient to detect 100% of blood cultures that were positive for a pathogenic organism. • Peterson & Abele (2005) discussed the use of bedside ultrasound for performing lumbar puncture (LP) when the traditional "blind" technique has been unsuccessful or is likely to be difficult. The authors address the successful use of diagnostic ultrasound-guided LP in the infant population. • A double-blind, randomized controlled trial conducted by the International Neonatal Immunotherapy Study (INIS) Collaborative Group (2011) evaluated the efficacy of adjunctive intravenous immune globulin (IVIG) in newborn infants receiving antibiotic therapy for proven or suspected sepsis. The placebo cohort included 1,734 infants and the IVIG group included 1,759 subjects. The IVIG group received initial dosing of 500 mg per kilogram which was repeated after 48 hours. A total of twenty-nine infants were excluded from the final analysis due to missing data. The authors concluded that the adjunctive use of polyvalent IgG immune globulin was not associated with any significant differences in risk of major complications or adverse outcomes in infants with suspected or proven sepsis. • Bizzarro et al (2015) evaluated the epidemiology and microbiology of neonatal sepsis in level IV neonatal intensive care units from 2004-2013. Sixty percent of the infants diagnosed with EOS were very low birth weight and Escherichia coli was identified as replacing group B streptococcus as the most common organism associated with EOS. During this time period the rates of EOS remained relatively stable at 0.9 per 1,000 live births. • Mukherjee et al (2015) evaluated the impact of the 2012 NICE guideline for managing early onset sepsis in the UK. This guideline called for a repeat C-reactive protein (CRP) 18-24 hours into treatment. This CRP measurement was intended to aid in determining the length of antibiotic treatment and the need for lumbar puncture (LP). The authors reported increased length of hospitalizations, longer durations of antibiotic treatment and an increase in lumbar punctures following the implementation of the NICE guideline. Even though the number of lumbar punctures increased from 14% to 23% after the NICE guideline, there were no positive LP results identified. • As part of the "Choosing Wisely" campaign Ho et al (2015) identified five tests and procedures in newborn medicine that contributed to health care waste. The authors reported that there was insufficient evidence to support antibiotic therapy longer than 48 hours in initially asymptomatic infants who do not display evidence of bacterial infection. The majority of pathologic organisms can now be identified via blood culture prior to 48 hours and extending the duration of antibiotic treatment may increase the risk for necrotizing

	enterocolitis and death in extremely low birthweight infants. • A retrospective cohort study by Kuppala et al (2011) showed prolonged empirical antibiotic administration to premature infants with negative blood cultures in the first week of life was associated with subsequent severe outcomes, LOS, NEC and increased mortality. • Mukhopadhyay et al (2015) examined the effect of EOS evaluations on early breastfeeding initiation in asymptomatic infants. The authors identified a significant association in delayed breastfeeding when a sepsis evaluation resulted in separation of the infant from their mother within the first two hours of birth. A parallel association with increased formula supplementation in the first 24 hours of life was also identified. • In 2010, the Centers for Disease Control and Prevention (CDC) updated their guideline on Prevention of Perinatal Group B Streptococcal Disease. This document provides recommendations pertaining to the secondary prevention of early-onset GBS in newborns and includes guidance on full and limited diagnostic evaluations for possible sepsis, antibiotic therapy and infant observation. Laboratory analysis is not considered necessary for an asymptomatic infant whose mother received adequate intrapartum antibiotic prophylaxis. • 2012 clinical report from the American Academy of Pediatrics attempted to establish an evidence-based approach to the Management of Neonates with Suspected or Proven Early-Onset Bacterial Sepsis. This document includes recommendations for diagnostic evaluations and the optimal treatment of these neonates. • The CDC does not include the measurement of acute phase reactants such as C-reactive protein (CRP) in their recommendations for full or limited sepsis evaluations due to the low sensitivity and specificity for detection of neonatal sepsis. (2010) • Polin et al (2012) discussed the use of acute-phase reactants in evaluating the neonate with suspected bacterial sepsis. They indicate normal CRP measurements may identify infants at low risk for bacterial sepsis but these values should not be used to determine the duration of antibiotic therapy in infants with elevated levels. • A systematic analysis by Meem et al (2011) identified C-reactive protein as one of the most widely studied biomarkers for neonatal infections but the methodologies and study designs of this research were highly variable. • Sivanandan et al (2011) indicate the use of ampicillin and an aminoglycoside is the recommended initial therapy in infants with suspected early-onset bacterial sepsis and/or meningitis where GBS and E. coli are the predominant organisms. They also conclude there is inadequate evidence from randomized trials to recommend any particular agent(s) for the treatment of late-onset sepsis. • Cuna et al (2014) investigated whether histologic chorioamnionitis (HCA) was associated with early onset clinical sepsis in the term newborn population. A retrospective record review of 3,417 term infants identified 3,029 infants who were asymptomatic with no risk factors for sepsis and 388 infants with risk factors and/or clinical signs of suspected sepsis who were admitted to NICU. Among the asymptomatic cohort admitted to the normal newborn nursery, 9.4% had evidence of HCA and none of these infants developed early onset

	clinical sepsis. The authors reported that an isolated finding of HCA in a healthy term infant would not warrant additional diagnostics or treatment. • Sarkar et al (2014) performed a retrospective review to evaluate whether intrapartum antibiotic therapy delayed the growth of organisms in blood cultures obtained for suspected early-onset neonatal sepsis. Based on the data obtained over a 13.5 years' time period, no difference in the incubation time to blood culture positivity was identified between infants with blood culture-proven early-onset sepsis whose mothers received intrapartum antibiotic therapy and those infants whose mothers did not. The authors concluded the utilization of maternal intrapartum antibiotic treatment did not result in a delay in blood culture positivity for early-onset neonatal sepsis. • A retrospective cohort study by Berardi et al (2014) was performed to assess how physical examination alone compared with physical examination in conjunction with laboratory evaluation in well-appearing infants ≥ 35 weeks' gestation at risk for early onset sepsis (EOS). The infants who were evaluated utilizing physical examination alone were found to have received less unnecessary antibiotics with a shorter hospitalization than the infants evaluated with adjunctive laboratory testing. EOS symptoms presented earlier than initial laboratory test results in 42/44 infants and severe EOS was diagnosed within the first six hours of life in all of the neonates evaluated. The authors also did not identify any increase in severe complications or risk of illness after hospital discharge of the physical examination alone cohort. • A review by Du Pont-Thibodeau et al (2014) outlined the management of neonatal sepsis in term newborns. The authors indicated there is consensus regarding the initiation of antibiotic therapy when neonatal sepsis is suspected; however, there is lack of consensus regarding the timing of antibiotic discontinuation and no clear consensus on the overall management of term neonates with sepsis. This document stresses the need for additional well-designed randomized controlled trials in order to develop evidenced-based guidelines for neonatal sepsis management. • A retrospective cohort study by Schulman et al (2015) evaluated antibiotic use in 52,061 NICU infants in California during 2013. The authors identified a 40-fold variation in the antibiotic prescribing practice throughout the 127 NICUs that were included in this study. Overuse of antibiotics was demonstrated among many of these units with administration for various conditions that lacked a well-defined indication. • Benitz et al (2015) provided an overview of the current management guidelines from the CDC and AAP for suspected early-onset sepsis. The authors indicated neither laboratory testing nor identification of maternal risk factors is effective in identifying infants with early-onset sepsis at the current time. An isolated abnormal laboratory result such as a blood count or C-reactive protein level in a well-appearing infant with negative blood cultures should not justify continuation of antibiotic therapy beyond 48 hours.

Appendix A

This algorithm relates to secondary prevention of early-onset GBS among newborns (Centers for Disease Control and Prevention, 2010)



* Full diagnostic evaluation includes a blood culture, a complete blood count (CBC) including white blood cell differential and platelet counts, chest radiograph (if respiratory abnormalities are present), and lumbar puncture (if patient is stable enough to tolerate procedure and sepsis is suspected).

† Antibiotic therapy should be directed toward the most common causes of neonatal sepsis, including intravenous ampicillin for GBS and coverage for other organisms (including *Escherichia coli* and other gram-negative pathogens) and should take into account local antibiotic resistance patterns.

§ Consultation with obstetric providers is important to determine the level of clinical suspicion for chorioamnionitis. Chorioamnionitis is diagnosed clinically and some of the signs are nonspecific.

¶ Limited evaluation includes blood culture (at birth) and CBC with differential and platelets (at birth and/or at 6–12 hours of life).

** See table 3 for indications for intrapartum GBS prophylaxis.

†† If signs of sepsis develop, a full diagnostic evaluation should be conducted and antibiotic therapy initiated.

§§ If ≥37 weeks' gestation, observation may occur at home after 24 hours if other discharge criteria have been met, access to medical care is readily available, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital for at least 48 hours and until discharge criteria are achieved.

¶¶ Some experts recommend a CBC with differential and platelets at age 6–12 hours.

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Revision History

The following are approved changes incorporated into the revision numbers indicated below.

Revision	Date	Description of Change
V1.0	05/16/2013	New guideline (MB)
V2.0	05/01/2014	Job Aid revised into Medical Necessity Clinical Guideline eliminating information on late-onset sepsis. (CE)
V2.0	09/08/2014	Will replace JA2229743 on 01/01/2015. (CE)
V3.0	05/05/2015	Annual review with update by RS. (CE)
V4.0	05/05/2016	Annual review with revisions by RS. Information on IVIG use, serial normal CBC and/or CRP test results and newer risk algorithms added. Criteria for lumbar puncture revised. (CE)
V5.0	05/05/2017	Annual review with revisions by AJ. Risk calculator and information on the management of an asymptomatic infant added. (Eckard, Cookie)
V5.1	05/04/2018	Annual review by AJ. Reference added. (CE)