Clinical Performance Guideline
Neonatal Resource Services
Early-Onset Neonatal Sepsis

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 infants 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.

<table>
<thead>
<tr>
<th>Background</th>
</tr>
</thead>
</table>
| 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 in infants hospitalized in the NICU versus <7 days in term infants, or late onset (LOS), occurring after 72 hours in NICU infants and after the first week of life in term infants. 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.  

Infants born preterm and 34 6/7 weeks and less because of cervical incompetence, preterm labor, PROM, chorioamnionitis, and/or acute or otherwise unexplained onset of nonreassuring fetal status are at highest risk for EOS. In these cases, infection could be the cause or preterm birth or a secondary complication from PROM and cervical dilatation.  

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)  

Delivery characteristics of extremely preterm infants can be used to identify those with significantly lower incidence of EOS. Recognition of differential risk may help guide decisions to limit early antibiotic use among approximately one-third of these infants. |
### Treatment Criteria

Clinical evidence in the medical literature supports the following:

- Newborns who exhibit signs of early-onset sepsis at birth or within the first 48 hours after birth should have the following evaluation performed:
  - Blood culture
  - Lumbar puncture if clinically indicated (e.g., positive blood culture, neurologic symptoms, failure to demonstrate clinical improvement). In critically ill preterm infants their physiologic stability, risk of EOB and potential harm of an extended antibiotic regime must be considered. (Puopolo, 2018)
  - Chest x-ray if the infant is presenting with altered respiratory status. Preterm infants commonly have cardiorespiratory instability and empirical antibiotic therapy should not be administered based solely on this indication. (Puopolo, 2018)

- 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. In severely ill preterm infants at highest risk for Gram-negative EOS and critically ill term infants, a broader spectrum antibiotic may be considered while waiting for culture results. Antimicrobial treatment should be narrowed to the specific pathogen(s) based on culture and sensitivity results. (Puopolo, 2018)

- Asymptomatic preterm infants at lower risk for EOS may be managed initially without any lab evaluation or empirical antibiotic therapy or they may be handled using a blood culture and clinical monitoring. Lower-risk preterm infants would include those who were delivered via cesarean section, those with obstetric indications for preterm birth and those deliveries without labor, attempts to induce labor or any ROM prior to delivery. (Puopolo, 2018)

- Asymptomatic preterm infants at higher risk for EOS many be managed with a blood culture and initiation of empirical antibiotic therapy. This cohort of preterm infants may include those with preterm birth due to cervical incompetence, PROM, preterm labor or chorioamnionitis/IAI. (Puopolo, 2018)

- 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)

- 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.

- Infants born preterm and 34 6/7 weeks and less because of cervical incompetence, preterm labor, PROM, chorioamnionitis, and/or acute or otherwise unexplained onset of nonreassuring fetal status are at highest risk for EOS. In these cases, infection could be the cause or preterm birth or a secondary complication from PROM and cervical dilatation. These infants should have a blood culture and empirical antibiotics started. Obtaining CSF for culture before administration of antibiotics should be considered if the infant will tolerate the procedure and if it will not delay administration of
antibiotics. (Puopolo 2018)

- 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 late-preterm and term infants ≥ 35 weeks’ gestation may be assessed for increased risk of EOS by categorical algorithms based on intrapartum risk factors, multivariate risk assessment based on intrapartum risk factors and infant exams (e.g., Neonatal Early-Onset Sepsis Risk Calculator: https://neonatalsepsiscalculator.kaiserpermanente.org/) or serial physical exams of the infant. (Puopolo, 2018)
- 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 by 36-48 hours of incubation if blood culture results are negative and the likelihood of sepsis is low. (Puopolo, 2018) 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.
- 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)
- Early discharge should be associated with close outpatient follow-up.

**Clinical Evidence**

- Two clinical reports from the AAP (2018) provided direction on the management of infants with suspected or proven EOS: one addressing the gestational age of ≤ 34 6/7 weeks and the other referring to a gestational age of ≥ 35 0/7 weeks. Because gestational age is the greatest sole predictor of EOS and the preterm population may have multiple risk factors for EOS, it is challenging to use risk stratification strategies in preterm infants. The degree of risk for EOS based on the circumstances of the preterm birth should be
weighed with the risk/benefit of empirical antibiotic therapy. Empirical antibiotics provided to very preterm infants shortly after birth, even in the absence of a positive blood culture, may increase the risk for poor patient outcomes. Blood culture continues to be the gold-standard for diagnosing EOS. Sequential abnormal lab values of CRP, procalcitonin and CBC should not be utilized for clinical decisions on extending antibiotic treatment for infants without a positive blood culture. Ampicillin and gentamicin are indicated as preferential empiric therapy agents for EOS.

- Puopolo (2018) provided an overview of Management of Neonates Born at less than or equal to 34 6/7 weeks Gestation With Suspected or Proven Early-Onset Bacterial Sepsis. Infants born preterm and 34 6/7 weeks and less because of cervical incompetence, preterm labor, PROM, chorioamnionitis, and/or acute or otherwise unexplained onset of nonreassuring fetal status are at highest risk for EOS. In these cases, infection could be the cause or preterm birth or a secondary complication from PROM and cervical dilatation. These infants should have a blood culture and empirical antibiotics started. Obtaining CSF for culture before administration of antibiotics should be considered if the infant will tolerate the procedure and if it will not delay administration of antibiotics.

- A facility-based Quality Improvement initiative was described by Joshi et al (2019). This effort kept well-appearing chorioamnionitis-exposed (CE) infants ≥ 35 weeks’ gestation with their mother while undergoing serial clinical examinations for symptoms of EOS. Of the 319 infants included in this study, 7.2% had laboratory testing performed and 4.7% received antibiotics. Only one infant was diagnosed with B Streptococcus EOS and treated 24 hours after birth. Results of this initiative reduced the number of infants receiving ampicillin from 12.3% to 5.1% and decreased the use of CRP from 16.6% to 7.6%. No adverse events were noted.

- A retrospective cohort study by Azuma & Boulais (2018) evaluated whether asymptomatic late preterm and term infants whose mother had chorioamnionitis should receive antibiotic therapy or clinical observation. Out of 240 infants who were observed in the mother-infant unit with CBC and hsCRP monitoring, only 78 required NICU admission and antibiotic treatment. Twelve of these infants had a true positive blood culture with only two presenting with clinical signs and symptoms of EOS. The authors concluded that asymptomatic chorioamnionitis-exposed infants may not necessarily require antibiotic treatment. A combination of clinical observation and lab monitoring for up to 34 hours may be an alternative management strategy but additional RCTs are needed to support these findings.

- A review by Hooven et al (2018) discussed recent clinical studies utilizing serial observation for asymptomatic term and late-preterm infants with risk factors for sepsis in lieu of empirical antibiotics. They indicated that the risk for EOS sepsis in chorioamnionitis-exposed infants varies drastically according to gestational age. EOS rates in moderate and extremely preterm infants are approximately 5-10 times higher than in infants who are ≥ 35 weeks’ gestation. In infants at lower risk of EOS, the current medical literature appears to suggest that serial observation may be a cost-effective and safe replacement strategy to lab testing and empiric antibiotics. Unnecessary admission to NICU disrupts the mother-infant connection and may result in delayed breastfeeding. There appears to be a shift in the optimal management for infants who are
considered at risk for EOS.

- Cantey et al (2017) performed a retrospective cohort study evaluating the risk of BPD in VLBW infants who had received empiric antibiotic therapy. Out of 1140 infants included in the study, 14 died and 557 developed BPD before the postmenstrual age of 36 weeks. The authors indicated that each additional day of antibiotic therapy in the first two weeks after birth increased the infants' risk of BPD by approximately 13%. They also were found to increase the severity of BPD and a combined outcome of BPD or death. The study describes BPD as an additional adverse outcome correlated with extended or unnecessary antibiotic administration. Although probiotics have been suggested as rescue therapy to return the gut microbiome to normal, antibiotic stewardship is stressed by the authors to reduce the incidence of adverse outcomes.

- An additional 2018 prospective cohort study by Cantey et al assessed the risk of NEC, late-onset sepsis or death following empiric antibiotic use in preterm VLBW infants. Among a cohort of 374 infants who received antibiotics in the first 14 days of life, 19% developed late-onset sepsis, NEC or death. Each additional day of antibiotic therapy also contributed to a 24% increased risk of the above adverse events. The authors provided supporting evidence on the risk of adverse outcomes when unwarranted antibiotics are administered to preterm VLBW infants.

- A review by Flannery & Puopolo (2018) assessed the efforts of unnecessary antibiotic usage and stressed the need for neonatal antimicrobial stewardship. Currently, there are no standardly accepted metrics of neonatal antimicrobial usage. The results of recent studies outlined the potential risks to both preterm and term infants as a result of unnecessary antibiotic exposure. For preterm infants the risks may include increased mortality, increased invasive fungal infections and resistant bacterial infections. For term infants there is a potential for maternal/infant separation affecting breastfeeding and increased exposure to pathogens in the NICU environment. Later in childhood, an increased risk of asthma has also been noted.

- Shulman et al (2018) performed a retrospective cohort study to identify the antibiotic use rate (AUR) in California NICUs. As a result of practice variations, the authors noted a reduction in antibiotic use between 2013 and 2016 with a decrease of 21.9% in the overall AUR. However, due to the lack of correlation between the AUR and proven infection or NEC, it was noted that the AUR could be reduced even further.

- An observational double-cohort study by Astorga et al (2018) assessed the effect of an automatic 48-hour stop order for gentamycin and ampicillin in one NICU. Antibiotic usage in a preintervention cohort (n=564) was compared to a postintervention cohort (n=639). The two cohorts were evenly matched in both maternal and fetal characteristics. During the preintervention period 54% of the infants received admission antibiotics. In the postintervention period 46% received admission antibiotics. Exposures per patient decreased by 30% for ampicillin and 38% for gentamycin. Cefotaxime, metronidazole and vancomycin were not included in the auto stop order but their usage was also noted to have decreased by 34%, 41.5% and 66% respectively.
• 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.

Bibliography

Azuma D & Boulais J. Does maternal chorioamnionitis have to equal antibiotics in an asymptomatic infant? J Perinatol. 2018;38:778-780.


American Academy of Pediatrics Committee on Fetus and Newborn and ACOG Committee on Obstetric Practice; Riley LE & Stark AR, editors. Guidelines for Perinatal Care, 7th ed. 2012.


Lefebvre CE, Renaud C, Chartrand C. Time to positivity of blood cultures in infants 0 to 90 days old presenting to the emergency department: Is 36 hours enough? J Pediatric Infect Dis Soc. 2015 Nov 29. pii: piv078.


Puopolo KM, Benitz WE, Zaoutis TE, AAP COMMITTEE ON FETUS AND NEWBORN, AAP COMMITTEE ON INFECTIOUS DISEASES. Management of Neonates Born at ≥35 0/7 Weeks’ Gestation With Suspected or Proven Early-Onset Bacterial Sepsis. Pediatrics. 2018;142(6):e20182894.


Terrin G. Ranitidine is associated with infection, necrotizing enterocolitis, and fatal outcome in newborns. Pediatrics, January 2012:129(1).


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

<table>
<thead>
<tr>
<th>Revision</th>
<th>Date</th>
<th>Description of Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1.0</td>
<td>05/16/2013</td>
<td>New guideline (MB)</td>
</tr>
<tr>
<td>V2.0</td>
<td>05/01/2014</td>
<td>Job Aid revised into Medical Necessity Clinical Guideline eliminating information on late-onset sepsis. (CE)</td>
</tr>
<tr>
<td>V2.0</td>
<td>09/08/2014</td>
<td>Will replace JA2229743 on 01/01/2015. (CE)</td>
</tr>
<tr>
<td>V3.0</td>
<td>05/05/2015</td>
<td>Annual review with update by RS. (CE)</td>
</tr>
<tr>
<td>V4.0</td>
<td>05/05/2016</td>
<td>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)</td>
</tr>
<tr>
<td>V4.0</td>
<td>05/05/2017</td>
<td>Annual review with revisions by AJ but this document is renewed without change at this time pending publication of revised guideline which will be effective 11/30/2017. (CE)</td>
</tr>
<tr>
<td>V5.0</td>
<td>11/30/2017</td>
<td>Revised guideline posted. Risk calculator and information on the management of an asymptomatic infant added. (CE)</td>
</tr>
<tr>
<td>V5.1</td>
<td>05/04/2018</td>
<td>Annual review by AJ. Reference added. (CE)</td>
</tr>
<tr>
<td>V6.0</td>
<td>05/04/2019</td>
<td>Annual review by AJ. The guideline criteria were revised to correlate with the recent AAP recommendations and older CDC recommendations were removed. The criterion extending antibiotic treatment based on persistently abnormal lab data was removed. Information on infants at highest risk for EOS, close outpatient follow-up after early discharge and discontinuation of antibiotics beginning at 36 hours of incubation when blood culture is negative was added. (CE)</td>
</tr>
</tbody>
</table>