Risk assessment, therapy and prevention of early-onset neonatal sepsis

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Risk Assessment, Therapy, and Prevention of Early-Onset Neonatal Sepsis

GRADUATION THESIS

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This graduation paper was made at the Department of Neonatology, Clinic for Obstetrics and Gynecology at the University Hospital Centre Zagreb under the supervision of Assist. Prof. Mirta Starčević, MD, PhD., and it was submitted for evaluation in the academic year 2022/2023.

The graduation paper was made at the Department of Neonatology, University of Zagreb School of Medicine.

Mentor: Assist. Prof. Mirta Starčević, MD, PhD

Abbreviations

AAP: American Academy of Pediatrics

CDC: Centers for Disease Control and Prevention

CRP: C-reactive Protein

CSF: Cerebrospinal Fluid

EOS: Early-Onset Neonatal Sepsis

GBS: Group B Streptococcus

IAP: Intrapartum Antibiotic Prophylaxis

IL-6: Interleukin-6

I/T: Immature to Total Neutrophil Ratio

LOS: Late-Onset Neonatal Sepsis

LP: Lumbar Puncture

NICE: National Institute for Health and Care Excellence

NICU: Neonatal Intensive Care Unit

PPROM: Preterm Premature Rupture of Membranes

PPV: Positive Predictive Value

PROM: Premature Rupture of Membranes

ROM: Rupture of Membranes

SRC: Sepsis Risk Calculator

TTP: Time to Positivity

VLBW: Very Low Birth Weight

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Summary

Risk Assessment, Therapy, and Prevention of Early-Onset Neonatal Sepsis

Matthias Kolonko

The heterogeneous presentation of early-onset sepsis (EOS) makes the early diagnosis and management of EOS in newborns a challenging task for neonatology healthcare teams. On one hand, early unspecific signs of EOS can be easily overlooked and on the other hand, unwarranted empiric treatment with antibiotics can have long-term negative health consequences for infants. Therefore, the management of neonates with suspected or culture-positive proven EOS requires standardized and evidence-based diagnostic and therapeutic approaches. The guidelines presented in this review include the most widely used and extensively researched recommendations on neonatal EOS from highly science-oriented national healthcare organizations, such as the Centers for Disease Control and Prevention (CDC), the American Academy of Pediatrics (AAP) in the United States, and the National Institute for Health and Care Excellence (NICE) in the UK. This review aims to compare and discuss the important role of up-to-date risk assessment tools for early-onset neonatal sepsis, such as the Kaiser Permanente Neonatal Sepsis Calculator (SRC), the NICE guidelines for neonatal infection, as well as modern neonatal sepsis treatment and prevention strategies.

KEYWORDS: Early-Onset Sepsis, Risk Assessment, Sepsis Risk Calculator, Antibiotic Treatment, Prevention

Sažetak

Rizični čimbenici, liječenje i prevencija rane novorođenačke sepse

Matthias Kolonko

Raznolikost kliničke prezentacije rane neonatalne sepse čini dijagnozu i liječenje izazovnim zadatkom za neonatološke zdravstvene timove. S jedne strane, rani nespecifični znakovi neonatalne sepse mogu se lako previdjeti, a s druge strane, neopravdano empirijsko liječenje antibioticima može imati dugoročne negativne zdravstvene posljedice za novorođenčad. Iz tog razloga, liječenje novorođenčadi sa sumnjom na ranu novorođenačku sepsu ili dokazanom infekcijom zahtijeva standardizirane dijagnostičke i terapijske postupke utemeljene na znanstvenih dokazima. Smjernice predstavljene u ovom diplomskom radu najčešće su korištene i opsežno istražene preporuke o pristupu neonatalnoj sepsi od visoko znanstveno orjentiranih nacionalnih zdravstvenih organizacija, kao što su Centers for Disease Control and Prevention (CDC) i American Academy of Pediatrics (AAP) u Sjedinjenim Američkim Državama, te National Institute for Health and Care Excellence (NICE) u Velikoj Britaniji. Ovaj diplomski rad ima za cilj usporediti i raspraviti važnost uloge suvremenih alata za procjenu rizika rane novorođenačke sepse, kao što su Kaiser Permanente kalkulator za novorođenačku sepsu ili NICE smjernice za neonatalnu infekciju, te prikazati moderne strategije prevencije i liječenja.

Ključne riječi: Rana novorođenačka sepsa, Rizični čimbenici, Kaiser Permanente Sepsis Risk Kalkulator, prevencija, liječenje

1. Introduction

In the 21st century, neonatal sepsis still represents a major cause of worldwide newborn mortality, affecting low-, middle- and high-income countries. Even with the technological progress in molecular diagnostics, the correct and prompt diagnosis of neonatal sepsis demands joint efforts and clinical expertise from the neonatology health care team and continues to be a challenging task in every neonatal intensive care unit (NICU). The Global Burden of Disease (GBD) Study 2017 approximated the incidence of neonatal sepsis to 1.3 million cases per year worldwide (1), leading to 203 000 sepsis-related deaths (2). In accordance with the Third International Consensus for Sepsis and Septic Shock (Sepsis-3), sepsis is "defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection" (3). The definition of neonatal sepsis is lacking such international consensus and relies on variable criteria to define this clinical syndrome in newborns.

Neonatal sepsis is generally characterized by systemic infection with multi-organ involvement, usually of bacterial etiology, occurring in infants during the first 28 days of life. It represents an important cause of newborn morbidity and mortality (4). In the United States, the CDC defines early-onset sepsis as a newborn infection with evidence of positive blood and/or CSF culture arising in the first 7 days of life (5,6). In general, EOS can be defined as a positive blood or CSF culture-proven infection accompanied by clinical signs indicative of neonatal systemic disease (7). Depending on the period of onset, neonatal sepsis can be distinguished between early-onset (EOS) or late-onset sepsis (LOS). The medical literature variably describes the time limits for EOS and LOS. The period for the diagnosis of EOS is usually considered in term infants with systemic infection within the first 7 days of life. LOS is defined as bacteriemia in newborns from day 8 to 28 (8).

Premature neonates and in general neonates in the NICU are at higher risk for developing EOS, which is in this group and specialized care setting congruously defined as sepsis occurring in the first 3 days (≤72h) of life (9,10). The etiology of EOS in term and preterm infants is mostly of bacterial origin acquired vertically from the mother before (in utero) or during delivery (intrapartum) (9,10). Even though EOS is in the majority of cases caused by bacterial pathogens, it may also be of fungal and viral etiology (11,12).

2. Epidemiology

The epidemiology of EOS differs significantly between low-/middle-income countries and high-income countries, as well as between term and preterm infants and different ethnicities. In the United States, the overall incidence of culture-positive EOS ranges between 0.77 to 1 per 1000 live births. The incidences of EOS in premature neonates weighing <1000g measure up to 26 per 1000 live births and in preterm infants weighing between 1000-1500g the incidence decreases to approximately 8 per 1000 live births. African American neonates in the US have a significantly higher risk of acquiring EOS with an estimated incidence of up to 0.89 per 1000 live births generally. In the same ethnicity, the preterm neonates are reaching a maximum rate of 5.14 per 1000 live births with a high fatality rate of 24.4% (10,13).

According to Giovanni et al.'s prospective population-based cohort study, the incidence of EOS in Switzerland is 0.28 per 1000 live births (95% CI 0.23-0.35) (14). In comparison with the above-mentioned incidence rate in the US, Switzerland has an up to 3-fold lower EOS incidence rate.

The mortality rate of neonatal sepsis may vary significantly between low-, middle- and high-income countries and preterm and term infants. In Sub-Saharan Africa, the mortality rates due to neonatal sepsis are approximated to be between 17 to 29 % (15). According to the epidemiologic systemic review and meta-analysis of Fleischmann et al., the global mortality due to neonatal sepsis, including EOS and LOS, is estimated to be 17.6% (95% CI 10.3% - 28.6%) (16). In the US, the mortality of late-preterm and term neonates with EOS is between 2-3 % (13,17). In premature infants with neonatal sepsis, especially in cases of VLBW, the mortality risk is significantly higher than in term neonates (9,10,18).

3. Etiology and Risk Factors

Group B Streptococcus (GBS) and *E. coli* are the causative pathogens for approximately 70% of EOS (10). GBS is the most frequent causative pathogen in EOS in term infants. Considering preterm and VLBW neonates, *E. coli* and other Gram-negative bacteria are the most common pathogens responsible for EOS (9). Stoll et al. (13) calculated in their national cohort study of 400 000 infants the percentage

distribution of different causative pathogens in EOS in the US. In their study, GBS was the number one pathogen in EOS cases overall accounting for 43%, followed by *E. coli* reaching 29%. Additional causative pathogens from their cohort study are listed in **Table 1** (13). While GBS is the most common EOS-causing pathogen overall, *E. coli* is primarily responsible for the mortality and morbidity related to early-onset neonatal sepsis (17).

Table 1. Causative pathogens and their percentage distribution (13)

Pathogen	**EOS %**
Gram-positive total	62
- **GBS**	**43**
- Viridans group streptococci	5
- S. aureus	2
- Enterococci	3
- Group A streptococci	2
- Coagulase-negative Staphylococci	<1
- Other Gram-positive (Strep. pneum., Listeria mono., etc.)	6
Gram-negative	37
- **E. coli**	**29**
- Haemophili	3
- Other gram-negative	5
Fungi	
- Candida albicans	<1
Total	100

The most common causative bacteria of EOS (*GBS, E. coli*), frequently colonize the female urogenital tract, thereby increasing the risk of infecting the maternal reproductive organs and amniotic fluid. When these bacteria move up the vaginal canal to the uterus, they may cause chorioamnionitis during pregnancy, leading to potential infection of the fetus in utero or of the neonate intrapartum (8). Risk factors for EOS can be divided into maternal risk factors and neonatal risk factors (**Table 2**). Maternal risk factors include ingestion of foods contaminated with *Listeria monocytogenes*, such as lunch meats and dairy products, potentially infecting the mother and consequently the neonate. Medical interventions during pregnancy, like cervical cerclage, and amniocentesis, might also introduce pathogens into the amniotic fluid, thereby causing amniotic fluid infection followed by an increased risk of

EOS (19). Clinical criteria for the diagnosis of chorioamnionitis are maternal fever, increased leukocytes (> 15000 WBC/mm^3), uterine fundal tenderness, purulent amniotic fluid, and maternal (>100 bpm) and fetal tachycardia (>160 bpm). Risk factors for developing chorioamnionitis include prolonged membrane rupture (PROM, and PPROM), prolonged labor, multiple digital vaginal examinations, internal monitoring, GBS colonization, and meconium-stained amniotic fluid (20). Intraamniotic infection may lead to EOS in 1% to 4% of newborns from mothers with proven infection (21,22). Several studies (23–25) show that the main risk factors for EOS in infants are premature birth, maternal GBS colonization, prolonged rupture of membranes >18h, and evidence of intraamniotic infection.

Table 2. **Maternal and neonatal risk factors for EOS** (8,10,26)

Maternal Risk Factors for EOS	Neonatal Risk Factors for EOS
Vaginal colonization with GBS	Prematurity and low birth weight
Prolonged rupture of membranes (>24h)	Fetal tachycardia
Intra-amniotic infection	Congenital anomalies
Maternal fever or leukocytosis	Complicated or instrument-assisted delivery
	Male sex
	Low APGAR scores (≤6 at 5 min)

4. Clinical presentation of EOS

Clinical indicators of EOS and the normal physiological transitions in newborns after delivery may correspond notably with each other making the diagnosis of EOS a demanding endeavor for neonatologists. Besides that, bacteremia in neonates may develop without showing any clinical signs, which could be indicative of systemic infection in the newborn (27,28). Newborns with EOS are usually not febrile upon presentation but show often signs of hypothermia. Other common nonspecific signs of EOS are grunting, abnormal crying, poor feeding, pallor, lethargy, anuria, and acidosis. Infants with EOS usually present with respiratory signs, such as apnea, tachypnea, nasal flaring, and increased work of breathing with intercostal retractions. Common cardiovascular signs are hypoxia, cyanosis, bradycardia, prolonged capillary refill time, poor perfusion, and hypotension. It is crucial to understand the importance of serial clinical assessment and monitoring of vital signs in ill-appearing neonates. Slight

alterations in cardiac and respiratory status, temperature instability, or poof feeding may be the first indicators of illness (8,10). A summary of the clinical indicators of EOS is displayed in **Table 3** (29).

Table 3. **Clinical indicators of EOS** (29)

Red flag clinical indicators:	
Apnea (temporary stopping of breathing)	Need for mechanical ventilation
Seizures	Signs of shock
Need for cardiopulmonary resuscitation	
Other clinical indicators (non-red-flag):	
Altered behavior or responsiveness	Persistent pulmonary hypertension
Altered muscle tone (e.g., floppiness)	Jaundice within 24 hours of birth
Feeding difficulties (e.g., feed refusal)	Signs of neonatal encephalopathy
Feed intolerance (e.g., vomiting, excessive gastric aspirates and abdominal distension)	Temperature abnormality (lower than 36°C or higher than 38°C) unexplained by environmental factors
Abnormal heart rate (bradycardia or tachycardia)	Unexplained excessive bleeding, thrombocytopenia, or abnormal coagulation
Signs of respiratory distress (e.g., grunting, recession, tachypnoea)	Altered glucose homeostasis (hypoglycemia or hyperglycemia)
Hypoxia (e.g., central cyanosis, reduced O2 saturation level)	Metabolic acidosis (base deficit of 10 mmol/liter or greater)

Preterm neonates present with a different clinical picture in comparison with term infants. Lim et al.'s retrospective case series study shows that EOS in preterm neonates frequently presents with initial signs of apnea, bradycardia, and cyanosis (65.8%), together with "poor activity" (48.7%) and increased respiratory work (43%) (18). In the majority of cases, the first sign of EOS in term neonates is respiratory distress, opening up a variety of potential differential diagnoses in the newborn, including congenital heart disease, respiratory distress syndrome (RDS), pneumothorax, transitory tachypnea, or congenital diaphragmatic hernia. Radiographic imaging with a chest X-ray and arterial blood gas analysis can detect or narrow down the diagnoses. The first signs of EOS in term newborns usually manifest within 6 to 24 hours after birth. In a mildly ill-appearing newborn, close monitoring for 6 hours is sufficient before invasive medical interventions are considered and applied if necessary. If the clinical status of the infant has stabilized after 6 hours, neonatal

sepsis is improbable. In case of clinical deterioration, the complete sepsis workup should be initiated and thoroughly performed (10).

5. Laboratory Investigations and Diagnosis of EOS

The sepsis workup includes a single blood culture, complete blood count with differential, urine culture, and a lumbar puncture for cerebrospinal fluid (CSF) count and culture (22,30). However, according to the recent guidelines for EOS laboratory investigation from the National Institute for Health and Care Excellence (NICE), urine culture and microscopy are not anymore routinely recommended, but a baseline C-reactive protein (CRP) concentration should be obtained for treatment guidance before starting antibiotics (29).

Blood culture: At present, the gold standard for diagnosing sepsis in newborns is the successful isolation of pathogens from a sterilely acquired blood culture (31,32). Studies show that the optimal blood volume for obtaining accurate blood culture results including cultures with a low colony count (<4 CFU/mL), amounts to a minimum of 1 mL of blood (33,34). Modern blood culture techniques with enriched culture media with antimicrobial neutralization effect can achieve positive results in less than 24 hours with a median time to positivity (TTP) of 11.17 hours for gram-negative organisms and a median TTP of 23.59 hours for gram-positive organisms (35,36). The study of Guerti et al. suggests: 1. to set the upper limit of incubation time to 3 days, 2. to prolong the incubation time to >3 days in blood samples taken from neonates <72h after birth, 3. to target antibiotic therapy exclusively to gram-positive organisms after 48 hours of a negative culture, and 4. to discontinue antimicrobial therapy in case of a negative blood culture after 72 hours of incubation in a well-appearing infant (36).

Differential blood count: The analysis of complete blood count with differential and absolute neutrophil counts and the ratio of immature to total neutrophils (I/T ratio) is a commonly used screening tool for neonatal infection. Yet, multiple studies consistently confirm unreliable sensitivity and specificity of these laboratory parameters for the diagnosis of EOS (37–39). In the cohort study conducted by Murphy and Weiner, they concluded that a combination of two sequential normal I/T neutrophil ratios with a negative blood culture at 24h could reliably exclude the diagnosis of EOS (negative

predictive value 100%; 95% CI: 99,905%-100%) and therefore suggest that antimicrobial therapy could be safely discontinued (40).

Lumbar puncture (LP): Concomitant meningitis is relatively common in neonates with sepsis. Approximately 23% of newborns with a positive blood culture have additional CSF infection with meningitis (41). The NICE guidelines recommend performing a lumbar puncture and CSF culture if “there is a strong clinical suspicion of early-onset neonatal infection” or “there are clinical symptoms or signs suggesting meningitis” (29). The AAP guidelines advise an LP in neonates with a positive blood culture, critical illness, or in those who do not respond to antibiotic treatment as expected (21,42). It is important to perform the LP before starting with the antimicrobial therapy to get accurate results from the CSF culture (43). However, the lumbar puncture should never pose any increased risk to the clinical condition or delay therapy in the critically-ill infant (42).

CRP/PCT and other biomarkers: The only sufficiently researched and applied biomarkers in the diagnosis and treatment of EOS are CRP and procalcitonin (PCT). Both CRP and PCT can be physiologically elevated up to 48 hours postpartum. In addition, both biomarkers take 6-8 hours to surge after the onset of infection and may show increased values in multiple other conditions (39). Therefore, these biomarkers are not helpful indicators of whether or not to initiate early antimicrobial treatment (28). However, the study of Benitz et al. shows that sequential normal CRP values can safely exclude infection in newborns with a negative predictive value of almost 100% (44). The 2021 NICE guidelines advise taking serial CRP measurements to facilitate decision-making on the duration of antibiotic therapy (29), whereas the AAP guidelines do not endorse CRP-guided antibiotic therapy duration. In a multicentre trial, the authors showed in their study that applying serial PCT values in directing antibiotic discontinuation significantly reduced the duration of antibiotic treatment and the length of hospital stay in neonates with EOS (45). The research conducted on acute-phase reactants in EOS emphasizes the importance of serial measurements of CRP and PCT as guidance for antibiotic discontinuation, with a baseline assessment early on and serial measurements 6-12 hours after the onset of illness in the neonate (10). Other biomarkers for EOS have been studied, such as interleukin 6, interleukin 8, gamma interferon (IFN), and tumor necrosis factor-alpha, but they are still not in routine clinical use for the diagnosis of EOS (10). Celik et al. investigated in their study the diagnostic value of the combination of IL-6 and CRP and observed a more reliable

detection of neonatal sepsis by considering both biomarkers in combination rather than using them individually (46). These results show potential promising and helpful applications of biomarkers for diagnosing and treating EOS in the near future.

Molecular Testing: Molecular testing methods as a diagnostic tool for neonatal sepsis are PCR- and DNA microarray-based methods. These modern molecular testing technologies could allow faster detection of pathogens with high sensitivity and specificity, and quicker application of targeted antimicrobial therapy. However, the relatively high cost and the limited amount of pathogens included in the testing kits still limit the wide use of these modern diagnostic techniques (10).

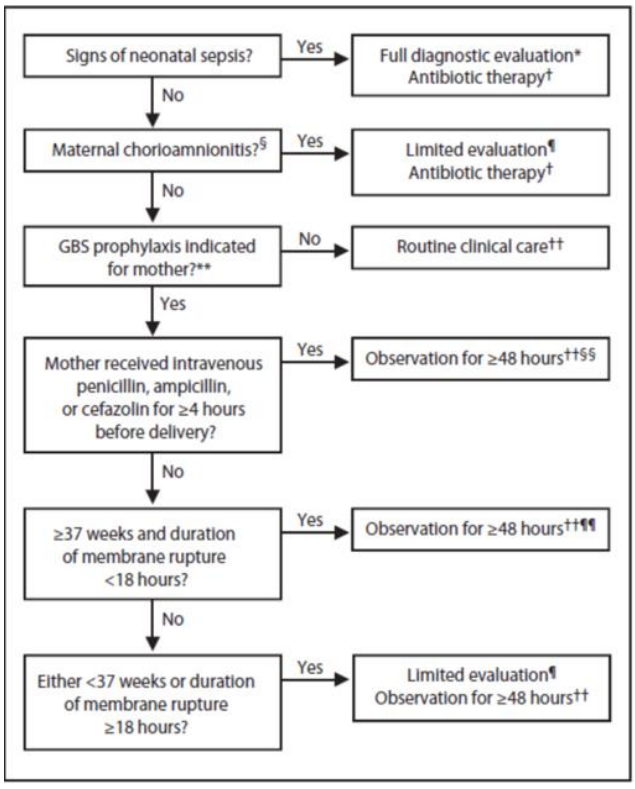
6. Risk assessment of EOS

Both the AAP and NICE guidelines have the common objective of correctly identifying and diagnosing those neonates with EOS and reducing the empirical antibiotic therapy in uninfected infants (28). The AAP recommends three different risk assessment strategies and associated management guidelines for neonates with suspected early-onset sepsis (42). The three currently used approaches of risk stratification for term and late-preterm infants in the US consist of categorical risk assessment, multivariate risk assessment, and risk assessment based on serial clinical examinations. Each risk assessment strategy has advantages and limitations and combining them may optimize the results in timely identifying and treating neonates with EOS or those who are at high risk of developing EOS. None of these approaches is suitable for identifying all newborns who will eventually acquire EOS or for preventing antimicrobial therapy in all those who will not develop sepsis. As a consequence, besides the risk assessment algorithms, each neonatology unit has to incorporate a neonatal observation and monitoring system for those newborns who seem initially well-appearing but are at risk of EOS and to reduce the duration of antibiotic therapy for those infants who turn out to be healthy. It is important to mention that each healthcare institution or system has to choose the appropriate risk assessment strategies and adapt them according to its internal resources and structures. Finally, an individual optimal approach should be scientifically measured and evaluated on a regional or national base in order to reduce adverse events and optimize efficacy in the detection and management of EOS (42).

6.1 Categorical Risk Assessment of EOS

The categorical risk assessment includes threshold values based on maternal risk factors and neonate clinical indicators to detect infants with increased risk for developing EOS (42). In the US, the CDC algorithms for primary and secondary prevention of EOS from group B streptococcal disease have been internationally used as a general basis for developing preventative measures for all etiologic types of EOS (23).

The CDC guidelines (5) for secondary EOS prevention incorporate risk factors with the following categories: 1. neonates with signs of sepsis, 2. neonates born to women with a diagnosis of intraamniotic infection, 3. a mother colonized with GBS but received inadequate intrapartum antibiotic prophylaxis (IAP), with prolonged ROM >18 hours or late preterm birth < 37 weeks of gestation, or 4. a mother positive for GBS with insufficient IAP but who does not have any other risk factors.



The CDC recommends a full diagnostic workup of the neonate (blood culture, CBC with differential and platelet counts, chest radiograph, LP) with empirical antibiotic therapy for Category 1, a limited laboratory evaluation (blood culture, CBC with differential and platelets) and antibiotic therapy for Category 2. Neonates in Category 3 should have a limited laboratory evaluation and clinical observation for ≥48 hours, and only clinical observations for ≥48 hours are indicated for Category 4 (**Figure 1**).

Figure 1: Secondary Prevention of EOS (5)

The CDC guidelines for GBS prevention have been continuously updated since 1996 and have been included internationally by neonatologists in local algorithms. Some limitations of using the categorical risk factor approach are inconsistent definitions of neonatal clinical disease and abnormal laboratory findings in the newborn, the complexity of diagnosing intraamniotic infection, and the different opinions on intrapartum antibiotics (42). However, there is substantial research data supporting the advantages and effectiveness of GBS-specific disease algorithms (23,47,48).

In the UK, the NICE guidelines present the major EOS screening tool. This neonatal infection algorithm is also a categorical model. It consists of confined values determining dichotomous outcomes giving risk factors with higher EOS significance (red flags) priority in the algorithm.

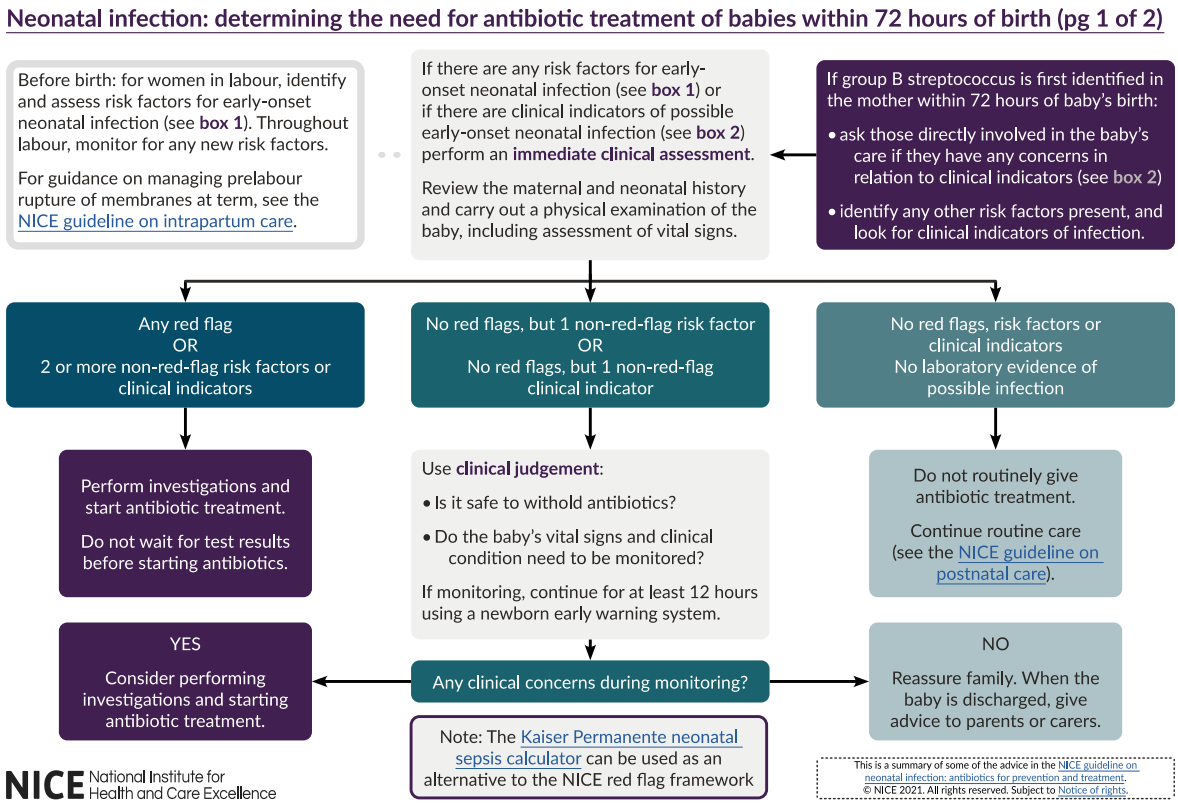


Figure 2: NICE - Neonatal Infection Algorithm (29)

The objective, as in the CDC guidelines, is the risk assessment and guidance in the empiric antibiotic treatment in neonates at risk of EOS (49). The NICE algorithm (see **Figure 2**) for neonatal infection includes ‘red flags` and ‘non-red flag` risk factors (see **Table 3**) and clinical indicators to decide which neonates need EOS workup and

treatment (29). In neonates who present one red flag or two or more non-red flag risk factors or clinical indicators, the NICE recommendations suggest performing clinical and laboratory workup and administration of empirical antibiotics immediately after blood culture collection. In newborns without red flags, but one single non-red flag risk factor or clinical indicator, clinical judgment should be used for the guidance of medical interventions. In case the neonate is not started on antibiotics, the NICE guidelines recommend clinical observation and monitoring for 12 hours by applying a newborn early warning system (28,29).

6.2 Multivariate Risk Assessment of EOS

The Kaiser Permanente Neonatal Early-Onset Sepsis Risk Calculator (SRC) is a multivariate risk assessment tool that synthesizes patient-specific risk factors and the neonate's clinical status to obtain an EOS risk score estimate of each newborn. Puopolo et al. developed a quantitative stratification model on the basis of a retrospective nested case-control study including data from a cohort of 608 014 live births with ≥34 weeks' gestational age at 14 US hospitals from 1993 to 2007. The study extracted out of this cohort 350 culture-positive EOS cases of neonates <72h of age and matched them with a control group of 1063 infants (50,51). The multivariate predictive model uses objective data from maternal and gestational factors, including gestational age, highest maternal antepartum temperature, ROM in hours, GBS status of mother (negative, positive, unknown), and the type of intrapartum antibiotics. This data calculates a prior EOS risk score per 1000/births. This general risk score is then integrated into the composite EOS risk comprising the neonate's clinical presentation (well-appearing, equivocal, clinical illness) that is classified by the infant's vital signs and clinical condition within the first 24 hours (52). The yielding composite EOS risk estimate (EOS risk at birth + clinical exam) grouped into three clinical presentations of the newborn (well-appearing, equivocal, clinical illness) guides the clinical management. The stratification of the EOS risk score with its resulting algorithm is shown in the following **Figure 3**.

Composite EOS Risk (EOS Risk at birth + Clinical Exam)	**Clinical Recommendation**	**Vital Signs Monitoring**

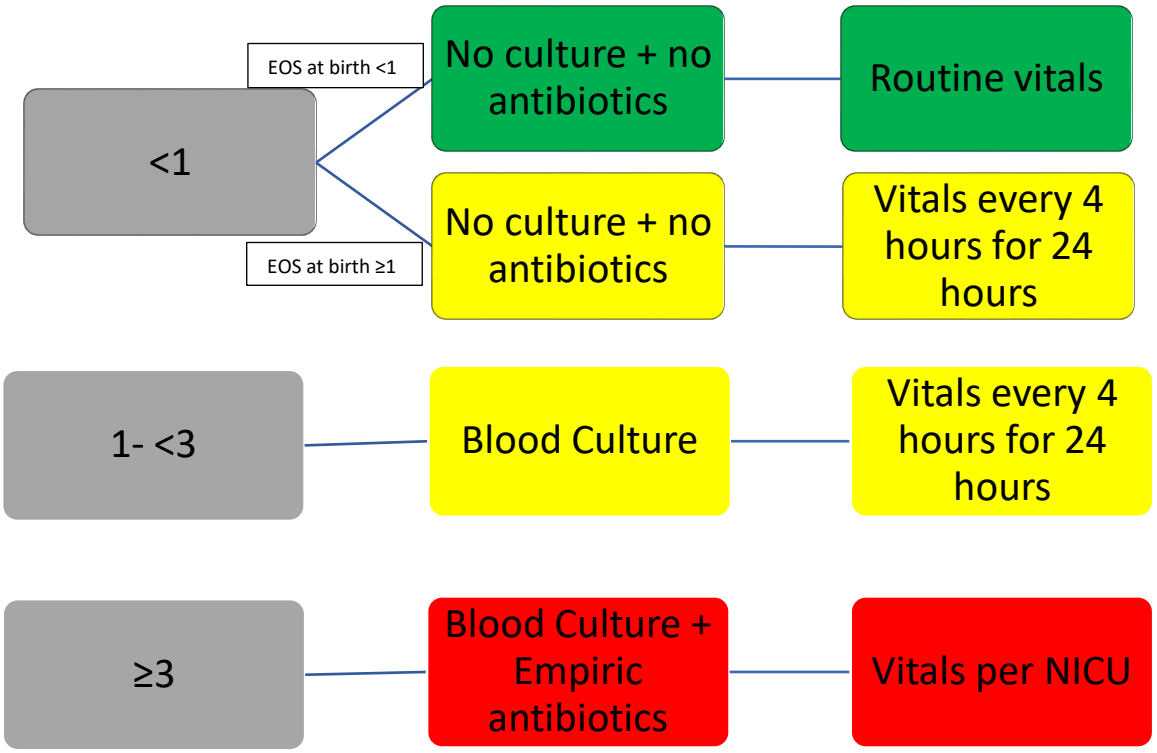


Figure 3: **The stratification of the EOS risk score in the Neonatal Sepsis Risk Calculator.** Diagram used and adapted from Kaiser Permanente Neonatal EOS Calculator Webpage (52).

Neonates with a composite EOS risk ≥1 per 1000 live births should receive a blood culture and enhanced monitoring of vital signs, and for infants with an EOS risk equal to and above 3 per 1000 live births, the clinical recommendations comprise blood culture and empirical antibiotics. Kuzniewicz et al. showed in their prospective validation with a study cohort of 204 685 infants that the application of the multivariate neonatal EOS risk calculator may result in the reduction of blood culture testing by 66% and of empirical antibiotic therapy by 48% in comparison with the prior use of the categorical risk assessment by the CDC (53). The application of the SRC showed no increased occurrence of adverse events during hospitalization. The number of readmissions for culture-positive neonatal sepsis after hospital discharge occurred only in about 5 per 100 000 births without any difference comparing the SRC versus the CDC algorithm (42,53). Another multicentre prospective observational projection study by Goel et al. compared the NICE guidelines with the Kaiser Permanente SRC. Their study demonstrated that the introduction of the SRC in the UK could decrease antibiotic therapy and other medical interventions in three out of four term and late-preterm neonates. They also showed that the SRC in combination with enhanced

clinical observations could enable earlier hospital discharge in more than 50% of treated infants (49). The following example of the SRC illustrates the application of objective clinical data and its results with clinical recommendations about blood culture, empirical antibiotic treatment, and vital signs monitoring (**Figure 4**) (52).

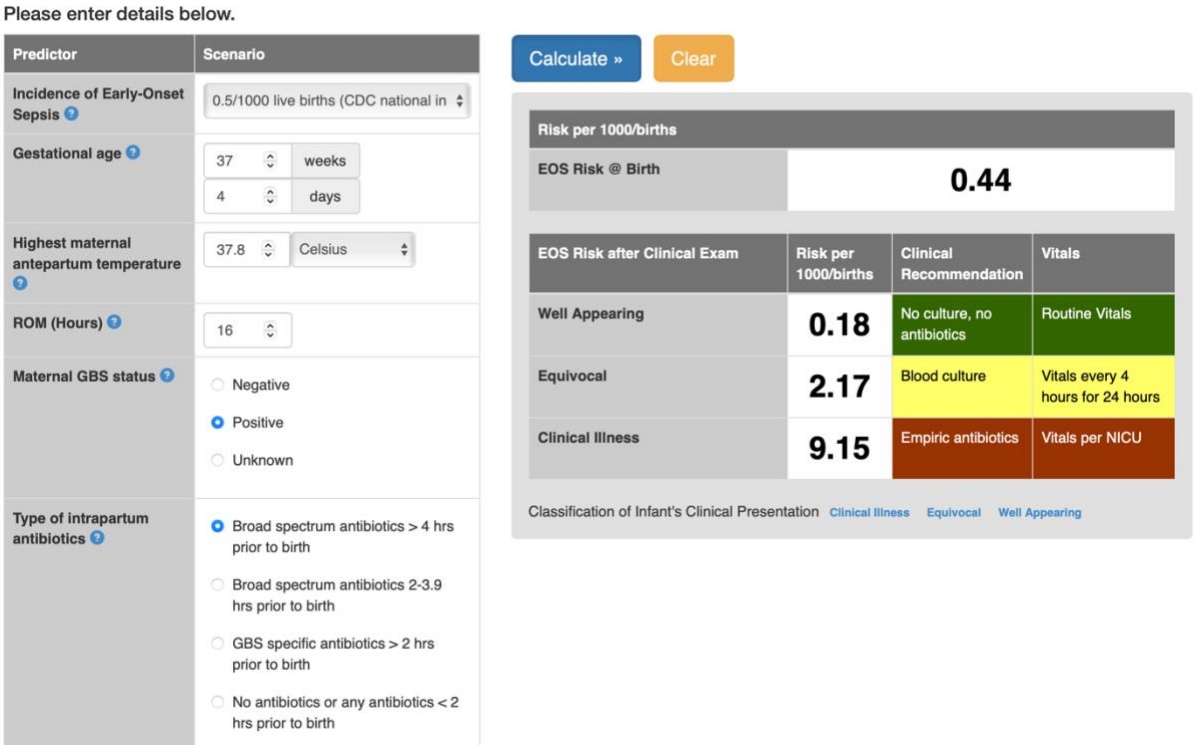


Figure 4: **Neonatal EOS Calculator**. With permission from Kaiser-Permanente Research Unit (52).

The major clinical benefits of the multivariate EOS calculator consist of the following: 1. the individualization of the newborn's EOS risk by combining categorical variables (GBS status, maternal intrapartum antibiotics), continuous variables (highest intrapartum temperature, gestational age, duration of ROM) and the newborn's clinical condition in the first 24 hours, 2. the use of only objective data without unreliable clinical diagnoses, such as intraamniotic infection applied in other algorithms, and 3. low empirical antibiotic treatment rates in neonates with a well-appearing clinical presentation. Some concerns about the implementation of the SRC may be the increased workload for the ongoing clinical observations of the newborns within the first 24 hours necessary for the classification of neonates as well-appearing, equivocal, or clinically ill (53,54). Another limitation of the SRC represents its non-applicability for preterm infants below 34 weeks of gestational age.

6.3 Risk Assessment Based on Serial Clinical Examinations

A third risk assessment strategy involves serial clinical observations to identify neonates with EOS. This approach does not include maternal and newborn risk factors, instead neonates who present with signs of illness at birth or develop clinical signs of EOS within the first 24 hours after birth receive a laboratory workup with blood culture and are empirically treated with antibiotics (42). Term and late-preterm neonates who present clinically well-appearing at birth with normal vital signs have a 60-70% risk reduction in developing EOS (50,53). Cantoni et al. compared in their prospective study the outcome between a cohort of 7628 term neonates evaluated by a categorical EOS risk factor approach plus standardized physical examinations and a cohort of 7611 infants receiving standardized physical examination only. The second cohort with standardized physical examination alone was associated with a significant decline in the use of laboratory workups, blood cultures, and antibiotic therapy. In the second cohort, two newborns who develop EOS were diagnosed on time when they started to show signs of illness by serial physical examinations performed every 4 to 6 hours within the first 48 hours of age (55). The AAP presents the following algorithm for managing risk assessment based on enhanced serial clinical examinations.

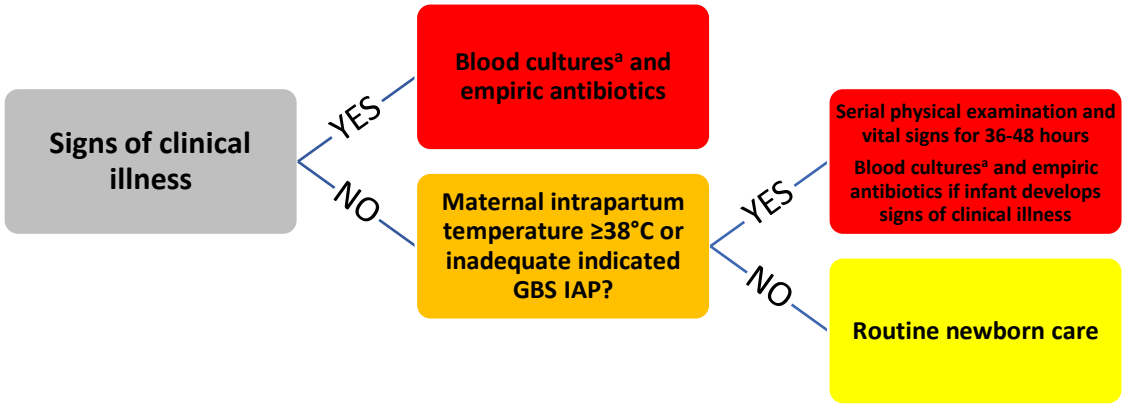


Figure 5: **Algorithm for serial clinical examinations**: a) consider LP and CSF culture before initiation of empiric antibiotics for infants who are at the highest risk of infection, especially those with critical illness (56).

Clinical centers that implement the EOS risk assessment approach of serial clinical observations need to create structures and trained nurses and doctors to provide an accurate and effective newborn assessment. The application of well-documented serial physical examinations and vital signs monitoring by NICU specialists ensures

prompt reactions to changes in the neonate's clinical condition and adequate management of infants with EOS (56).

7. Therapy of EOS

The AAP recommends a combination of intravenous ampicillin and gentamicin as the first-line empiric antibiotic therapy, with an additional synergistic effect against GBS and *Listeria monocytogenes* (21,57). Gentamicin may be effectively replaced with a third-generation cephalosporin (eg. cefotaxime). Yet, studies showed rapidly increasing resistance in the case of routine and prolonged administration of cefotaxime for neonatal infections (58) and it additionally increases the risk of invasive candida infections (59). Cefotaxime has a very effective CSF penetration and its administration should be therefore restricted to neonates with gram-negative meningitis (60). The administration of Ceftriaxone in neonates is not recommended by the AAP because it is readily bound to proteins and may increase unbound bilirubin by displacing it from proteins, with the potential risk of causing encephalopathic kernicterus (21). Neonates with EOS in the absence of a specific focus should receive antibiotic therapy for 10 days (61). GBS-specific uncomplicated meningitis is treated for at least 14 days (62). In the case of Gram-negative meningitis, neonates are treated for at least 21 days or 14 days if a subsequent culture proves to be negative. Antibiotic therapy in Gram-negative meningitis should be a combination of cefotaxime and gentamicin as long as the antimicrobial susceptibility testing results are pending (21,61,62). The NICE guidelines vary slightly in comparison with the AAP recommendations. The intravenous administration of benzylpenicillin with gentamicin represents the first-line empiric therapy for suspected EOS unless there is a local resistance for any of these antibiotics which would necessitate a different antimicrobial agent. Benzylpenicillin has a narrower spectrum of antibiotic activity than ampicillin. Penicillin is considered by NICE a more adequate choice for empiric therapy initiation in EOS to reduce antibiotic resistance. Gentamicin should be administered with a starting dose of 5mg/kg every 36 hours. Shorter intervals for gentamicin are indicated in case of a very ill-appearing infant or if the blood culture reveals a Gram-negative infection. It is important to perform therapeutic monitoring to measure blood gentamicin concentrations due to its nephrotoxicity and ototoxicity. In case of a proven Gram-negative infection,

benzylpenicillin should be stopped and may be replaced by cefotaxime. The NICE guidelines suggest antibiotic therapy for a duration of 7 days for neonates with culture-proven EOS, and for those with negative blood culture if EOS is strongly suspected. After 7 days antibiotics may be continued in case of an infant who has not yet entirely recovered or a specific pathogen has been identified requiring a longer duration of antibiotic treatment. In infants receiving antibiotics due to EOS risk factors or clinical indicators of suspected infection, antibiotic therapy should be ceased after 36 hours if: 1. the blood culture is still negative, 2. the neonate is in good clinical condition and well-appearing, or 3. the CRP levels are reassuring. In infants with suspected meningitis but unknown causative pathogens, the combination of intravenous amoxicillin and cefotaxime is indicated. If Gram-negative meningitis is confirmed, amoxicillin should be stopped, and treatment with only cefotaxime is recommended. For neonates with a CSF culture positive for GBS, the antibiotic treatment should include benzylpenicillin 50mg/kg every 12 hours for at least 14 days and gentamicin 5mg/kg every 36 hours for 5 days (29). The antimicrobial treatment for specific pathogens in neonatal infections according to UpToDate recommendations is shown in the following **Table 4** (63).

Table 4: **Pathogen-specific antibiotic therapy** (63)

Group B *Streptococcus*	Penicillin G
E. coli – Ampicillin-sensitive	Ampicillin
E. coli – Ampicillin-resistant	Expanded-spectrum cephalosporin (eg, ceftazidime, cefepime, or cefotaxime) Alternative: Meropenem
Multidrug-resistant gram-negative bacilli (including ESBL-producing organisms)	Meropenem
L. monocytogenes	Ampicillin and gentamicin
MSSA	Nafcillin/oxacillin or cefazolin
MRSA	Vancomycin
Coagulase-negative staphylococci	Vancomycin

Frequently, the culture may be negative, and the pathogen remains unidentified due to maternal antibiotic treatment or other factors. Though, the neonate may show obvious clinical signs of EOS. In these circumstances, empiric antibiotic management of the newborn usually for 10 days is started along with continuous vital signs monitoring (10,21). Serial WBC and CRP measurements can be used to assess the

severity of the neonatal infection and the response to therapy (64). In case the blood culture, drawn before antibiotic administration, remains negative and the neonate presents clinically well-appearing, antimicrobial therapy may be stopped at 48 hours to prevent adverse outcomes associated with prolonged empirical treatment (21). Infants with EOS usually improve clinically with antibiotic therapy within 24 to 48 hours (21). In general, laboratory parameters including WBC count, I/T ratio, and the CRP level generally normalize within 72 hours (65). Repeated blood and CSF cultures after antimicrobial treatment tend to be negative at 72 hours (66). It is recommended to repeat blood cultures within 24 hours of the expected effective treatment response. This follow-up testing is important to document clearance and guide therapy. Continuous positive cultures may require adjustments in antibiotic coverage and duration or indicate additional foci of infections, including bone, soft tissue, joint infections, or endocarditis. Further follow-up diagnostics include CRP levels, WBC counts, and I/T ratios which help to evaluate response to treatment (66).

8. Prevention of EOS

Maternal GBS colonization is the major risk factor for EOS in neonates (5). A study showed that maternal GBS colonization during pregnancy increases the newborn's risk of acquiring EOS disease by a factor of >25 (67). Without treatment of GBS colonized mothers, approximately 1-2% of neonates develop EOS (5,67). In total 10-30% of pregnant women have vaginal or rectal colonization with GBS (68). Therefore, the primary prevention of GBS-specific EOS is of great importance. The only evidence-based management to reduce the EOS incidence involves universal screening of pregnant women and IAP to prevent maternal GBS infection and reduce transmission to the newborn (5). The adequate IAP is defined by the administration of the antibiotic agent ≥4 hours before delivery. Both culture- and risk-based screenings can be applied to identify candidates for IAP. An extensively conducted population-based study revealed that culture-based testing is more effective than the risk-based method in preventing neonatal GBS disease. The culture-based screening proved to be more accurate in identifying women who are colonized with GBS and at higher risk of transmitting the bacteria to their infants (48). The timing of GBS screening is important. The GBS colonization status can alternate during pregnancy and the GBS culture is

most accurate if taken ≤5 weeks with a vaginal-rectal swab before parturition having a negative predictive value of 95-98% (69).

According to the CDC, universal GBS screening should be performed at a gestational age of 35-37 weeks (5). The CDC indications for IAP are: 1. positive prenatal cultures or positive PCR screening tests for GBS, 2. unknown maternal GBS status with gestation <37 weeks, ROM >18 hours, maternal antepartum temperature >38°C, 3. GBS bacteriuria during the current pregnancy, and 4. a previously delivered newborn with systemic GBS infection (5,21). The CDC recommends the following antibiotic regimens and dosing for IAP administration (**Figure 6**).

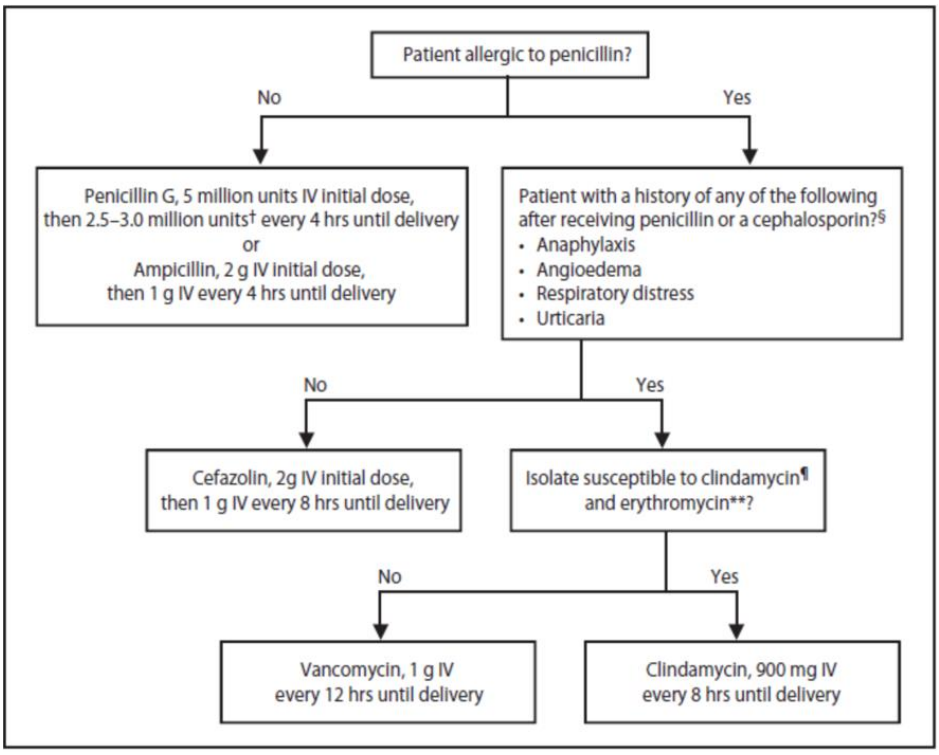


Figure 6: Antibiotic regiment for intrapartum antibiotic prophylaxis (5)

The first-line therapy for women with GBS-positive cultures or with unknown GBS status is penicillin (see **Fig. 6**). Antibiotic treatment recommendations for mothers with mild penicillin allergy include cefazolin, or with a history of significant allergic reactions to penicillin are Clindamycin and Vancomycin (5). Since the implementation of universal screening and IAP, the development of antibiotic resistance and an increased occurrence of gram-negative EOS have been a major concern (70). Ecker et al. confirm this concern in their study by demonstrating the growing numbers of Gram-negative and *Candida* infections and the rising resistance to ampicillin in *E. coli* infections since the introduction of IAP. The study showed by using regression

analysis that the growing resistance to ampicillin and penicillin is temporally connected with IAP (71). However, it is important to mention that as a result of extensive efforts in prevention measures, such as the IAP, the incidence of GBS-specific neonatal infections has decreased markedly in the US in the last decades, from 1.7 per 1000 live births at the beginning of the 1990s to 0.34 cases per 1000 live births in recent years (5). In the near future, a GBS vaccine may be a potent solution to avoid increasing antibiotic resistance and potentially eradicate neonatal GBS sepsis. Recently, research in GBS vaccine development has been intensified and there is a GBS polysaccharide vaccine in a phase 3 trial (72). The European Union launched and funded the DEVANI (Design a Vaccine against Neonatal Infections) project with the objective of developing a maternal immunization program to reduce the neonatal GBS disease burden. This project estimated a potential reduction of preterm births by up to 4% and a decline in stillbirths by up to 10% by the introduction of a GBS-specific vaccine (73). Besides IAP and potential GBS vaccines, the investments and efforts in providing optimal quality prenatal care for all women would further reduce neonatal sepsis and the associated morbidity and mortality (10).

9. Conclusions

Antibiotic management for neonatal EOS is in most countries similarly organized with only slight differences in the choice of antimicrobial agents and duration of therapy. The universal antepartum screening for GBS is at the present time the most effective strategy for the prevention of GBS disease in newborns and is superior to risk-based approaches for maternal IAP (74). The risk assessment and diagnosis of EOS in newborns still represent a complex task in our modern times. The introduction of EOS risk assessment algorithms has importantly contributed to the process of standardization of diagnostic and therapeutic EOS management strategies with the potential of significantly reducing empirical antibiotic use and hospital length of stay in infants. Neonatal healthcare centers around the world may use and combine different evidence-based existing guidelines and adapt them according to their local demands and settings.

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11. References

1. Vos T, Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet. 2017 Sep;390(10100):1211–59.

2. Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018 Nov;392(10159):1736–88.

3. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):801–10.

4. Krugman S. Krugman's Infectious Diseases of Children. Mosby; 2004. 1080 p.

5. Verani JR, McGee L, Schrag SJ, Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC). Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010. MMWR Recomm Rep Morb Mortal Wkly Rep Recomm Rep. 2010 Nov 19;59(RR-10):1–36.

6. Cotten CM. Antibiotic Stewardship: Reassessment of Guidelines for Management of Neonatal Sepsis. Clin Perinatol. 2015 Mar;42(1):195–x.

7. Mukhopadhyay S, Puopolo KM. Risk Assessment in Neonatal Early-Onset Sepsis. Semin Perinatol. 2012 Dec;36(6):408–15.

8. Marcdante K, Kliegman RM. Nelson Essentials of Pediatrics. Elsevier Health Sciences; 2018. 840 p.

9. Hornik CP, Fort P, Clark RH, Watt K, Benjamin DK, Smith PB, et al. Early and Late Onset Sepsis in Very-Low-Birth-Weight Infants from a Large Group of Neonatal Intensive Care Units. Early Hum Dev. 2012 May;88(Suppl 2):S69–74.

10. Simonsen KA, Anderson-Berry AL, Delair SF, Davies HD. Early-Onset Neonatal Sepsis. Clin Microbiol Rev. 2014 Jan;27(1):21–47.

11. Lin TY, Kao HT, Hsieh SH, Huang YC, Chiu CH, Chou YH, et al. Neonatal enterovirus infections: emphasis on risk factors of severe and fatal infections. Pediatr Infect Dis J. 2003 Oct;22(10):889–94.

12. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Changes in pathogens causing early-onset sepsis in very-low-birth-weight infants. N Engl J Med. 2002 Jul 25;347(4):240–7.

13. Weston EJ, Pondo T, Lewis MM, Martell-Cleary P, Morin C, Jewell B, et al. The Burden of Invasive Early-Onset Neonatal Sepsis in the United States, 2005–2008. Pediatr Infect Dis J. 2011 Nov;30(11):937–41.

14. Giannoni E, Agyeman PKA, Stocker M, Posfay-Barbe KM, Heininger U, Spycher BD, et al. Neonatal Sepsis of Early Onset, and Hospital-Acquired and Community-Acquired Late Onset: A Prospective Population-Based Cohort Study. J Pediatr. 2018 Oct;201:106-114.e4.

15. Ranjeva SL, Warf BC, Schiff SJ. Economic burden of neonatal sepsis in sub-Saharan Africa. BMJ Glob Health. 2018 Jan 1;3(1):e000347.

16. Fleischmann C, Reichert F, Cassini A, Horner R, Harder T, Markwart R, et al. Global incidence and mortality of neonatal sepsis: a systematic review and meta-analysis. Arch Dis Child. 2021 Aug;106(8):745–52.

17. Schrag SJ, Farley MM, Petit S, Reingold A, Weston EJ, Pondo T, et al. Epidemiology of Invasive Early-Onset Neonatal Sepsis, 2005 to 2014. Pediatrics. 2016 Dec;138(6):e20162013.

18. Lim WH, Lien R, Huang YC, Chiang MC, Fu RH, Chu SM, et al. Prevalence and pathogen distribution of neonatal sepsis among very-low-birth-weight infants. Pediatr Neonatol. 2012 Aug;53(4):228–34.

19. Gibbs RS, Duff P. Progress in pathogenesis and management of clinical intraamniotic infection. Am J Obstet Gynecol. 1991 May;164(5 Pt 1):1317–26.

20. Tita ATN, Andrews WW. Diagnosis and Management of Clinical Chorioamnionitis. Clin Perinatol. 2010 Jun;37(2):339–54.

21. Polin RA, Committee on Fetus and Newborn. Management of neonates with suspected or proven early-onset bacterial sepsis. Pediatrics. 2012 May;129(5):1006–15.

22. Edwards MS. Clinical features, evaluation, and diagnosis of sepsis in term and late preterm neonates - UpToDate [Internet]. 2013 [cited 2023 Feb 24]. Available from: https://www.uptodate.com/contents/clinical-features-evaluation-and-diagnosis-of-sepsis-in-term-and-late-preterm-neonates

23. Schuchat A, Zywicki SS, Dinsmoor MJ, Mercer B, Romaguera J, O'Sullivan MJ, et al. Risk factors and opportunities for prevention of early-onset neonatal sepsis: a multicenter case-control study. Pediatrics. 2000 Jan;105(1 Pt 1):21–6.

24. Schrag SJ, Hadler JL, Arnold KE, Martell-Cleary P, Reingold A, Schuchat A. Risk factors for invasive, early-onset Escherichia coli infections in the era of widespread intrapartum antibiotic use. Pediatrics. 2006 Aug;118(2):570–6.

25. Martius JA, Roos T, Gora B, Oehler MK, Schrod L, Papadopoulos T, et al. Risk factors associated with early-onset sepsis in premature infants. Eur J Obstet Gynecol Reprod Biol. 1999 Aug;85(2):151–8.

26. Benitz WE, Gould JB, Druzin ML. Risk factors for early-onset group B streptococcal sepsis: estimation of odds ratios by critical literature review. Pediatrics. 1999 Jun;103(6):e77.

27. Ottolini MC, Lundgren K, Mirkinson LJ, Cason S, Ottolini MG. Utility of complete blood count and blood culture screening to diagnose neonatal sepsis in the asymptomatic at risk newborn. Pediatr Infect Dis J. 2003 May;22(5):430–4.

28. Fleiss N, Schwabenbauer K, Randis TM, Polin RA. What's new in the management of neonatal early-onset sepsis? Arch Dis Child Fetal Neonatal Ed. 2023 Jan;108(1):10–4.

29. Recommendations | Neonatal infection: antibiotics for prevention and treatment | Guidance | NICE [Internet]. NICE; 2021 [cited 2023 Mar 3]. Available from: https://www.nice.org.uk/guidance/ng195/chapter/recommendations#investigations-before-starting-antibiotics-in-babies-who-may-have-early-onset-infection

30. Johnson CE, Whitwell JK, Pethe K, Saxena K, Super DM. Term newborns who are at risk for sepsis: are lumbar punctures necessary? Pediatrics. 1997 Apr;99(4):E10.

31. Puopolo KM, Mukhopadhay S, Frymoyer A, Benitz WE. The Term Newborn: Early-Onset Sepsis. Clin Perinatol. 2021 Aug;48(3):471–84.

32. Sabui T, Tudehope DI, Tilse M. Clinical significance of quantitative blood cultures in newborn infants. J Paediatr Child Health. 1999 Dec;35(6):578–81.

33. Schelonka RL, Chai MK, Yoder BA, Hensley D, Brockett RM, Ascher DP. Volume of blood required to detect common neonatal pathogens. J Pediatr. 1996 Aug;129(2):275–8.

34. Woodford EC, Dhudasia MB, Puopolo KM, Skerritt LA, Bhavsar M, DeLuca J, et al. Neonatal Blood Culture Inoculant Volume: Feasibility and Challenges. Pediatr Res. 2021 Nov;90(5):1086–92.

35. Garcia-Prats JA, Cooper TR, Schneider VF, Stager CE, Hansen TN. Rapid detection of microorganisms in blood cultures of newborn infants utilizing an automated blood culture system. Pediatrics. 2000 Mar;105(3 Pt 1):523–7.

36. Guerti K, Devos H, Ieven MM, Mahieu LM. Time to positivity of neonatal blood cultures: fast and furious? J Med Microbiol. 2011 Apr;60(Pt 4):446–53.

37. Newman TB, Puopolo KM, Wi S, Draper D, Escobar GJ. Interpreting complete blood counts soon after birth in newborns at risk for sepsis. Pediatrics. 2010 Nov;126(5):903–9.

38. Hornik CP, Benjamin DK, Becker KC, Benjamin DK, Li J, Clark RH, et al. Use of the complete blood cell count in early-onset neonatal sepsis. Pediatr Infect Dis J. 2012 Aug;31(8):799–802.

39. Benitz WE. Adjunct laboratory tests in the diagnosis of early-onset neonatal sepsis. Clin Perinatol. 2010 Jun;37(2):421–38.

40. Murphy K, Weiner J. Use of leukocyte counts in evaluation of early-onset neonatal sepsis. Pediatr Infect Dis J. 2012 Jan;31(1):16–9.

41. Isaacs D, Barfield CP, Grimwood K, McPhee AJ, Minutillo C, Tudehope DI. Systemic bacterial and fungal infections in infants in Australian neonatal units. Australian Study Group for Neonatal Infections. Med J Aust. 1995 Feb 20;162(4):198–201.

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

43. Garges HP, Moody MA, Cotten CM, Smith PB, Tiffany KF, Lenfestey R, et al. Neonatal meningitis: what is the correlation among cerebrospinal fluid cultures, blood cultures, and cerebrospinal fluid parameters? Pediatrics. 2006 Apr;117(4):1094–100.

44. Benitz WE, Han MY, Madan A, Ramachandra P. Serial serum C-reactive protein levels in the diagnosis of neonatal infection. Pediatrics. 1998 Oct;102(4):E41.

45. Stocker M, van Herk W, El Helou S, Dutta S, Fontana MS, Schuerman FABA, et al. Procalcitonin-guided decision making for duration of antibiotic therapy in neonates with suspected early-onset sepsis: a multicentre, randomised controlled trial (NeoPIns). Lancet Lond Engl. 2017 Aug 26;390(10097):871–81.

46. Celik IH, Demirel FG, Uras N, Oguz SS, Erdeve O, Biyikli Z, et al. What are the cut-off levels for IL-6 and CRP in neonatal sepsis? J Clin Lab Anal. 2010;24(6):407–12.

47. Schrag SJ, Zywicki S, Farley MM, Reingold AL, Harrison LH, Lefkowitz LB, et al. Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis. N Engl J Med. 2000 Jan 6;342(1):15–20.

48. Schrag SJ, Zell ER, Lynfield R, Roome A, Arnold KE, Craig AS, et al. A population-based comparison of strategies to prevent early-onset group B streptococcal disease in neonates. N Engl J Med. 2002 Jul 25;347(4):233–9.

49. Goel N, Shrestha S, Smith R, Mehta A, Ketty M, Muxworthy H, et al. Screening for early onset neonatal sepsis: NICE guidance-based practice versus projected application of the Kaiser Permanente sepsis risk calculator in the UK population. Arch Dis Child Fetal Neonatal Ed. 2020 Mar;105(2):118–22.

50. Escobar GJ, Puopolo KM, Wi S, Turk BJ, Kuzniewicz MW, Walsh EM, et al. Stratification of Risk of Early-Onset Sepsis in Newborns ≥34 Weeks' Gestation. Pediatrics. 2014 Jan;133(1):30–6.

51. Puopolo KM, Draper D, Wi S, Newman TB, Zupancic J, Lieberman E, et al. Estimating the Probability of Neonatal Early-Onset Infection on the Basis of Maternal Risk Factors. Pediatrics. 2011 Nov;128(5):e1155–63.

52. Northern California Kaiser-Permanente Neonatal Early-Onset Sepsis Calculator. [Internet]. [cited 2023 May 20]. Available from: https://neonatalsepsiscalculator.kaiserpermanente.org/

53. Kuzniewicz MW, Puopolo KM, Fischer A, Walsh EM, Li S, Newman TB, et al. A Quantitative, Risk-Based Approach to the Management of Neonatal Early-Onset Sepsis. JAMA Pediatr. 2017 Apr 1;171(4):365–71.

54. Dhudasia MB, Mukhopadhyay S, Puopolo KM. Implementation of the Sepsis Risk Calculator at an Academic Birth Hospital. Hosp Pediatr. 2018 May;8(5):243–50.

55. Cantoni L, Ronfani L, Da Riol R, Demarini S, Perinatal Study Group of the Region Friuli-Venezia Giulia. Physical examination instead of laboratory tests for most infants born to mothers colonized with group B Streptococcus: support for the Centers for Disease Control and Prevention's 2010 recommendations. J Pediatr. 2013 Aug;163(2):568–73.

56. Puopolo KM, Lynfield R, Cummings JJ, COMMITTEE ON FETUS AND NEWBORN, COMMITTEE ON INFECTIOUS DISEASES. Management of Infants at Risk for Group B Streptococcal Disease. Pediatrics. 2019 Aug;144(2):e20191881.

57. Baker CN, Thornsberry C, Facklam RR. Synergism, killing kinetics, and antimicrobial susceptibility of group A and B streptococci. Antimicrob Agents Chemother. 1981 May;19(5):716–25.

58. Bryan CS, John JF, Pai MS, Austin TL. Gentamicin vs cefotaxime for therapy of neonatal sepsis. Relationship to drug resistance. Am J Dis Child 1960. 1985 Nov;139(11):1086–9.

59. Manzoni P, Farina D, Leonessa M, d'Oulx EA, Galletto P, Mostert M, et al. Risk factors for progression to invasive fungal infection in preterm neonates with fungal colonization. Pediatrics. 2006 Dec;118(6):2359–64.

60. Bégué P, Floret D, Mallet E, Raynaud EJ, Safran C, Sarlangues J, et al. Pharmacokinetics and clinical evaluation of cefotaxime in children suffering with purulent meningitis. J Antimicrob Chemother. 1984 Sep;14 Suppl B:161–5.

61. Remington JS, Klein JO, Nizet V, Maldonado Y, Wilson CB. Infectious Diseases of the Fetus and Newborn Infant. Saunders/Elsevier; 2011. 1260 p.

62. Pickering LK, Pediatrics AA of. Red Book: 2009 Report of the Committee on Infectious Diseases. American Academy of Pediatrics; 2009. 984 p.

63. Antibiotic regimens for neonatal sepsis - UpToDate [Internet]. [cited 2023 Jun 7]. Available from: https://www.uptodate.com/contents/image?imageKey=PEDS%2F102574

64. Pourcyrous M, Bada HS, Korones SB, Baselski V, Wong SP. Significance of serial C-reactive protein responses in neonatal infection and other disorders. Pediatrics. 1993 Sep;92(3):431–5.

65. Gerdes JS. Diagnosis and management of bacterial infections in the neonate. Pediatr Clin North Am. 2004 Aug;51(4):939–59, viii–ix.

66. Joseph B Cantey, MD, MPH, Joseph A Garcia-Prats, MD, Morven S Edwards, MD. Management and outcome of sepsis in term and late preterm neonates - UpToDate [Internet]. [cited 2023 Jun 7]. Available from: https://www.uptodate.com/contents/management-and-outcome-of-sepsis-in-term-and-late-preterm-neonates

67. Boyer KM, Gotoff SP. Strategies for chemoprophylaxis of GBS early-onset infections. Antibiot Chemother. 1985;35:267–80.

68. Regan JA, Klebanoff MA, Nugent RP. The epidemiology of group B streptococcal colonization in pregnancy. Vaginal Infections and Prematurity Study Group. Obstet Gynecol. 1991 Apr;77(4):604–10.

69. Yancey MK, Schuchat A, Brown LK, Ventura VL, Markenson GR. The accuracy of late antenatal screening cultures in predicting genital group B streptococcal colonization at delivery. Obstet Gynecol. 1996 Nov;88(5):811–5.

70. Manning SD, Foxman B, Pierson CL, Tallman P, Baker CJ, Pearlman MD. Correlates of antibiotic-resistant group B streptococcus isolated from pregnant women. Obstet Gynecol. 2003 Jan;101(1):74–9.

71. Ecker KL, Donohue PK, Kim KS, Shepard JA, Aucott SW. The impact of group B streptococcus prophylaxis on late-onset neonatal infections. J Perinatol Off J Calif Perinat Assoc. 2013 Mar;33(3):206–11.

72. Edwards MS, Gonik B. Preventing the broad spectrum of perinatal morbidity and mortality through group B streptococcal vaccination. Vaccine. 2013 Aug 28;31 Suppl 4:D66-71.

73. Rodriguez-Granger J, Alvargonzalez JC, Berardi A, Berner R, Kunze M, Hufnagel M, et al. Prevention of group B streptococcal neonatal disease revisited. The DEVANI European project. Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol. 2012 Sep;31(9):2097–104.

74. Hasperhoven GF, Al-Nasiry S, Bekker V, Villamor E, Kramer B. Universal screening versus risk-based protocols for antibiotic prophylaxis during childbirth to prevent early-onset group B streptococcal disease: a systematic review and meta-analysis. BJOG Int J Obstet Gynaecol. 2020 May;127(6):680–91.

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