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Original Article

Utility of the Neonatal Early-Onset Sepsis Calculator in a Low-Risk Population

Kelley M. Sonney, DO[1] Dakota Tomasini, DO[1] James K. Aden, PhD[1] Caitlin M. Drumm, MD[2]

[1] Department of Pediatrics, Brooke Army Medical Center, Fort Sam Houston, Texas
[2] Department of Pediatrics, Uniformed Services University of the Health Sciences, Bethesda, Maryland

Address for correspondence Kelley M. Sonney, DO, Brooke Army Medical Center, 3551 Roger Brooke Dr., Fort Sam Houston, TX 78234-4504 (e-mail: kelleymburch@gmail.com).

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Abstract

Objective To compare early-onset sepsis (EOS) risk estimation and recommendations for infectious evaluation and/or empiric antibiotics using a categorical risk assessment versus the Neonatal Early-Onset Sepsis Calculator in a low-risk population.

Study Design Retrospective chart review of late preterm ($\geq 35^{0/7}$–$36^{6/7}$ weeks' gestational age) and term infants born at the Brooke Army Medical Center between January 1, 2012 and August 29, 2019. We evaluated those born via cesarean section with rupture of membranes (ROM) < 10 minutes. Statistical analysis was performed to compare recommendations from a categorical risk assessment versus the calculator.

Results We identified 1,187 infants who met inclusion criteria. A blood culture was obtained within 72 hours after birth from 234 (19.7%) infants and 170 (14.3%) received antibiotics per routine clinical practice, using categorical risk assessment. Respiratory distress was the most common indication for evaluation, occurring in 173 (14.6%) of patients. After applying the Neonatal Early-Onset Sepsis Calculator to this population, the recommendation was to obtain a blood culture on 166 (14%), to start or strongly consider starting empiric antibiotics on 164 (13.8%), and no culture or antibiotics on 1,021 (86%). Utilizing calculator recommendations would have led to a reduction in frequency of blood culture (19.7 vs. 14%, $p < 0.0001$) but no reduction in empiric antibiotics (14.3 vs. 13.8%, $p = 0.53$). There were no cases of culture-proven EOS.

Conclusion This population is low risk for development of EOS; however, 19.7% received an evaluation for infection and 14.3% received antibiotics. Utilization of the Neonatal Early-Onset Sepsis Risk Calculator would have led to a significant reduction in the evaluation for EOS but no reduction in antibiotic exposure. Consideration of delivery mode and indication for delivery may be beneficial to include in risk assessments for EOS.

Keywords
- infections
- newborn
- neonatal sepsis
- antimicrobial stewardship
- risk assessment

Key Points

- Cesarean section with rupture of membranes at delivery confers low risk for EOS.
- Respiratory distress often triggers an EOS evaluation.
- Delivery mode should be considered in EOS risk.

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Background

The overall incidence of neonatal early-onset sepsis (EOS) in the United States has drastically decreased with the introduction of guidelines for universal maternal Group B Streptococcus (GBS) screening and intrapartum antibiotic prophylaxis. However, EOS remains a high-consequence disease with significant morbidity and mortality among affected infants.[1] The current treatment regimen of antibiotics for infants undergoing EOS evaluation is not without adverse effects, such as increased risk for NEC, obesity, and acute kidney injury (AKI).[2–6] Thus, clinicians continue to seek the most effective ways to determine the risk of EOS while balancing the consequences of evaluations for EOS and exposure to empiric antibiotic treatment.

Recently, it has been shown that infants born with specific delivery characteristics (i.e., cesarean delivery without labor or membrane rupture before delivery, no evidence of intraamniotic infection, and no evidence of nonreassuring fetal status) are at extremely low risk of developing EOS. Two separate cohorts revealed zero cases of culture-proven EOS in infants meeting criteria for these low-risk delivery characteristics.[7,8] However, patients delivered via cesarean section (C/S) without labor are known to be at increased risk for respiratory distress.[9–13] Respiratory status factors heavily into a patient's clinical assessment and can trigger an evaluation for EOS and initiation of empiric antibiotics when using any of the three currently recommended approaches to EOS risk assessment: categorical risk assessment, multivariate risk assessment (the Neonatal Early-Onset Sepsis Calculator), and enhanced observation.[14]

Contemporary efforts to more accurately identify infants at risk for EOS revolve primarily around the utilization of multivariate risk assessment via the Neonatal Early-Onset Sepsis Calculator. Since its introduction, the calculator has been shown to substantially reduce the use of empiric antibiotics for suspected EOS.[15] However, the calculator currently does not factor mode or indication for delivery into risk assessment determination.[14] Due to this limitation, we hypothesize that the Neonatal Early-Onset Sepsis Calculator may commonly recommend a laboratory evaluation for EOS and empiric antibiotic treatment in a presumably low-risk population of neonates born via C/S with rupture of membranes (ROM) less than 10 minutes. The aim of this study was to compare rates of initiation of laboratory evaluations for EOS and/or empiric antibiotic use via categorical risk assessment, as used in routine clinical practice, versus the Neonatal Early-Onset Sepsis Calculator in a low-risk population at the Brooke Army Medical Center (BAMC) in San Antonio, TX.

Methods

This study is a secondary analysis of the retrospective data presented in "Early Antibiotic Exposure in Low-Risk Late Preterm and Term Infants" by Sonney et al.[7] All late preterm ($\geq 35^{0/7}$–$36^{6/7}$ weeks' gestational age) and term ($\geq 37^{0/7}$ weeks' gestational age) infants born at the BAMC via C/S with ROM less than 10 minutes, between January 1, 2012, and August 29, 2019, were identified and their medical records reviewed. As previously detailed, ROM less than 10 minutes was chosen as a surrogate for absence of labor since the presence or absence of labor was not consistently documented in the electronic medical record. Patients who were born to mothers with intraamniotic infection, who were transferred to another facility <4 days after birth, or those with congenital anomalies associated with empiric antibiotic use (e.g., gastroschisis, open neural tube defects) were excluded. BAMC is a large military treatment facility, which houses both a labor and delivery unit and a level III neonatal intensive care unit (NICU). The BAMC labor and delivery unit has an average of 1,800 deliveries per year. During the study period, BAMC utilized a categorical risk assessment method to guide clinical decision-making pertaining to EOS in the nursery.[16]

Pertinent patient demographics collected include maternal medications, maternal GBS status, highest maternal temperature, neonate sex, gestational age at birth, birth weight, length of stay, admission to the NICU, respiratory support, sepsis screen, and antibiotic administration. Due to the inability to accurately access vital sign level granularity from all patient charts, we presumed that infants delivered late preterm or term with ROM less than 10 minutes, no diagnosis of maternal intraamniotic infection, and admission to the nursery with no pertinent admission diagnoses would have been considered low risk for EOS via the Neonatal Early-Onset Sepsis Calculator. We utilized the presence of laboratory evaluation for EOS, respiratory distress diagnosis, utilization of respiratory support, diagnosis of hypothermia, or NICU admission to isolate patients that would have been categorized as "equivocal" or "clinical illness" by the Neonatal Early-Onset Sepsis Calculator. Patients potentially categorized as "equivocal" or "clinical illness" were identified and individually assessed using the Neonatal Early-Onset Sepsis Calculator via the free web-based tool (https://neonatalsepsiscalculator.kaiserpermanente.org/). The incidence of EOS used in the web-based tool was 0.5 per 1,000 live births. Resultant recommendations for either observation, blood culture only, or blood culture and empiric antibiotic initiation were then recorded. These recommendations were compared to actual patient management, as guided by the categorical risk assessment algorithm utilized in routine clinical practice during the study period.[16] EOS was defined as culture-proven bacteremia or bacterial meningitis occurring within 72 hours after birth. Early antibiotic exposure was defined as the administration of antibiotics within 72 hours after birth.

Statistical Analysis

Statistical analysis was performed to identify differences between patients who received antibiotics within 72 hours after birth and those who did not. Continuous variables were analyzed by using the Wilcoxon's rank sum test and a McNemar's test was performed for categorical data to compare the results of the categorical risk assessment and the Neonatal Early-Onset Sepsis Calculator via JMP v13.2 (SAS

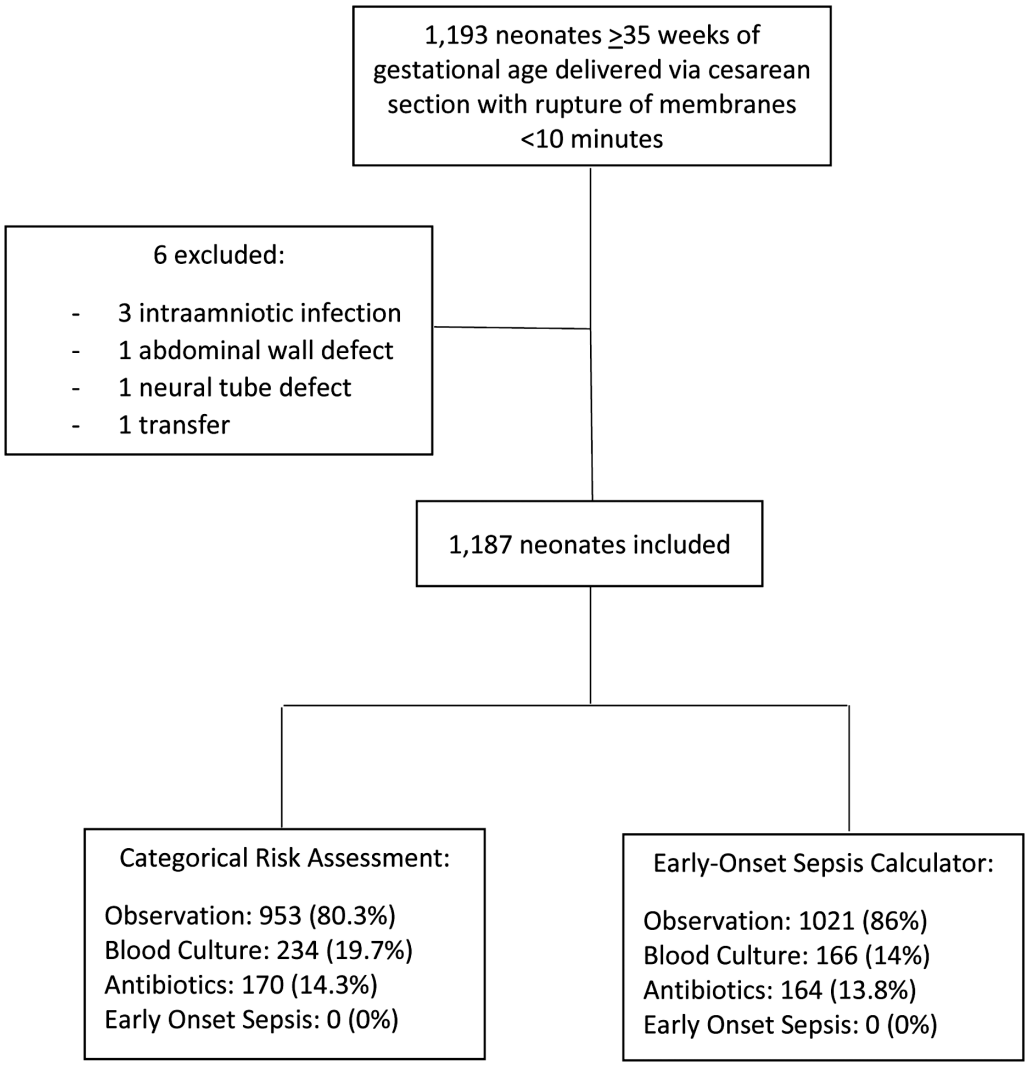

Fig. 1 Flow diagram of the study population.

Corp, Cary, NC). We considered $p < 0.05$ to be significant. This study was deemed exempt by the BAMC Institutional Review Board.

Results

We identified 1,187 infants who met inclusion criteria, (►**Fig. 1**). Within the course of routine clinical practice, guided by the categorical risk assessment algorithm, a blood culture was drawn within 72 hours after birth on 234 (19.7%) infants, and of those, 170 (14.3%) received empiric antibiotics. Of the 64 infants who had a blood culture drawn without initiation of antibiotics, the most common diagnosis was respiratory distress (54.6%) followed by hypoglycemia (35.9%). As described in the previous study,[7] respiratory distress was the most common indication for early blood culture and antibiotic initiation, (►**Fig. 2**). Among the entire cohort, 173 (14.6%) patients had a diagnosis of respiratory distress and 162 (13.7%) required respiratory support. Respiratory distress was the indication for blood culture in 167 (71.4%) of the 234 evaluations for EOS and the indication for initiation of antibiotics in 133 (78.2%) of the 170 infants exposed to antibiotics.

We then identified a cohort of 247 infants who underwent evaluations for EOS, had a diagnosis of respiratory distress or hypothermia, required respiratory support or NICU admission. These infants were presumed to meet criteria for either "equivocal" or "clinical illness" designation via the Neonatal Early-Onset Sepsis Calculator. After application of these patient variables to the Neonatal Early-Onset Sepsis Calculator, the multivariate risk assessment recommendation was to "strongly consider starting empiric antibiotics" or "empiric antibiotics" on 164 (13.8%), to obtain a blood culture on 166 (14%) and "no culture, no antibiotics" on 81 (7%) infants. The remaining 940 infants within the cohort did not undergo an evaluation for EOS, had no documented diagnoses consistent with equivocal status or clinical illness, and remained in the well newborn nursery. These 940 infants were presumed to have been deemed low risk with no recommendation for culture or antibiotics via the Neonatal Early-Onset Sepsis Calculator. Utilizing the Neonatal Early-Onset Sepsis Calculator recommendations would have led to a statistically

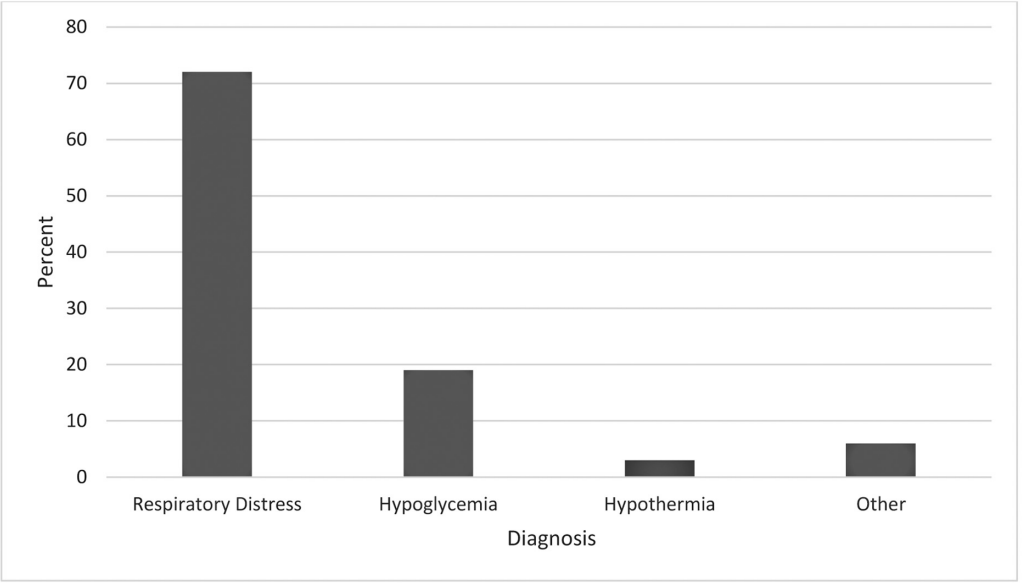

Fig. 2 Indication for laboratory evaluation for EOS using the categorical risk assessment. EOS, early onset sepsis.

significant reduction in the frequency of obtaining blood cultures (19.7 vs. 14%, $p < 0.0001$) but no significant reduction in empiric antibiotic exposure (14.3 vs. 13.8%, $p = 0.53$, ►**Fig. 3**). On an individual level, use of the Neonatal Early-Onset Sepsis Calculator would have eliminated antibiotic exposure in 48 infants, 26 of whom underwent a laboratory evaluation for EOS and empiric antibiotic treatment due to hypoglycemia. Conversely, the calculator recommended strong consideration for starting empiric antibiotics in 43 infants who did not receive antibiotics, a recommendation driven by respiratory distress symptoms within the clinical illness classification. We identified one patient within the cohort with a positive blood culture that grew *Micrococcus luteus*, which was deemed a contaminant. There were no cases of blood or cerebrospinal fluid culture-proven EOS.

Discussion

One in seven neonates in our low-risk cohort would have undergone a laboratory evaluation for EOS and received the

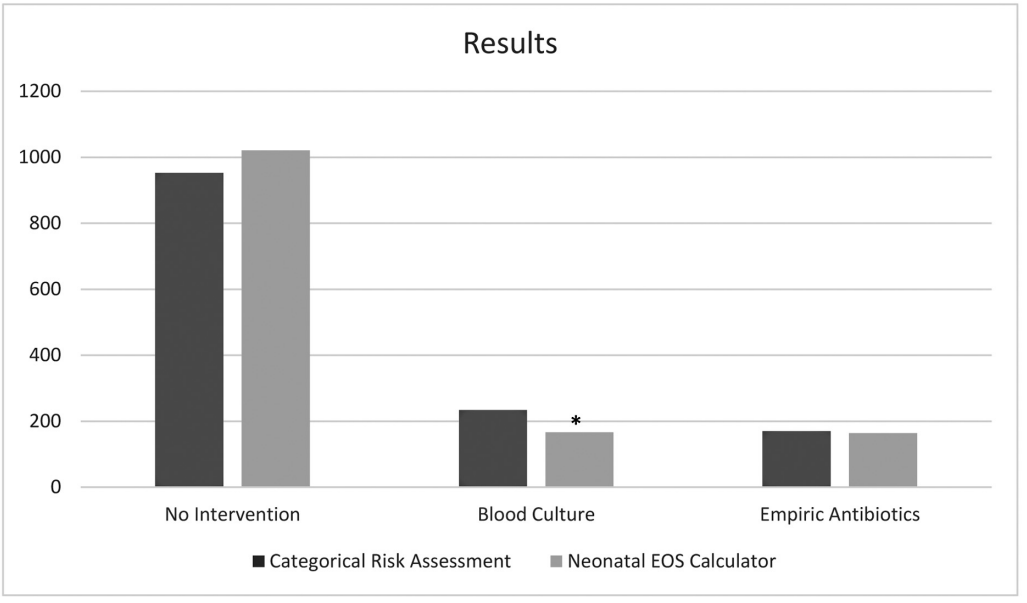

Fig. 3 Recommendations per categorical risk assessment versus neonatal early-onset sepsis calculator. *p-Value <0.0001.

recommendation to strongly consider initiation of antibiotics or empiric antibiotics per the Neonatal Early-Onset Sepsis Calculator. Utilizing the calculator, as opposed to the categorical risk assessment, would have led to a 5.7% reduction in sepsis work up but no reduction in antibiotic exposure in this cohort. While the results for reduction in laboratory evaluation for EOS are significant, in a cohort with zero cases of culture-proven EOS, there is still room for improvement in targeted antibiotic utilization.

The three currently recommended assessment tools utilized to determine risk of EOS in newborns support the predictive value of maternal GBS colonization, gestational age, maternal temperature, and duration of ROM to generate a risk assessment and guide provider decision-making. Appropriately, all three methods of assessment rely heavily on a clinical impression of the patient for final recommendations, which often results in the initiation of empiric antibiotics for abnormal vital signs or signs of clinical illness.[14] Infants born via C/S without labor are known to be at higher risk for noninfectious respiratory morbidity.[9–13] As in our cohort, these patients often require respiratory support outside of the delivery room, a marker of clinical illness and an indication for empiric antibiotic treatment using any of the three currently recommended EOS assessment tools. Within our cohort, 14.6% of neonates had a diagnosis of respiratory distress and 13.7% required respiratory support outside of the delivery room. As was expected, this respiratory morbidity was the primary driver for laboratory evaluations for EOS and antibiotic treatment. Despite this significant percentage of symptomatic patients, there were zero cases of culture-proven sepsis.

Of note, the Neonatal Early-Onset Sepsis Calculator did lead to a reduction in antibiotic exposure specifically for infants who previously had undergone a laboratory evaluation for EOS and empiric antibiotic treatment due to hypoglycemia. Twenty-six (43%) neonates who underwent a laboratory evaluation for EOS and empiric antibiotic treatment for hypoglycemia would have avoided both by utilizing the Neonatal Early-onset Sepsis Risk Calculator. Per the most recent guidelines on management of infants at risk for GBS disease, there is no evidence that isolated hypoglycemia is an otherwise asymptomatic neonate is a risk factor for EOS.[14]

While lifesaving in the face of true sepsis, empiric antibiotic exposure in uninfected newborns is not without risk. Studies continue to substantiate both the short- and long-term consequences of early antibiotic exposure.[2] An association has been demonstrated between preterm infants exposed to early antibiotics and later development of necrotizing enterocolitis.[3,4] Aminoglycosides, such as gentamicin, are commonly used for empiric coverage of EOS and have the potential to be nephrotoxic, leading to complications such as AKI, electrolyte disturbances, and fluid imbalances.[5] Early antibiotic exposure has been linked to increased risk for obesity later in life, possibly due to disruptions in intestinal microbiota.[6]

Evaluations for EOS and empiric antibiotics can lead to increased health care utilization and costs due to lab draws, antibiotic usage, and longer duration of patient stay.[17] Additionally, some hospitals require NICU admission for neonates undergoing a laboratory evaluation for EOS and empiric antibiotic coverage, further increasing financial burden.[18] Early separation of the mother–infant dyad to perform EOS evaluations has been shown to result in delayed initiation of breastfeeding and increased formula usage on the first day of life.[19] Additionally, it is important to acknowledge the potential impact of dyad separation and parental stress associated with EOS evaluations and NICU admission.[20,21]

Risk stratification utilizing the Neonatal Early-onset Sepsis Calculator has been shown to be safe and effective in reducing antibiotic exposure in neonates at risk for EOS.[15] However, due to the frequent occurrence of respiratory distress symptoms in neonates delivered via C/S without labor, this specific cohort remains at risk for considerable antibiotic overexposure, regardless of the utilized risk assessment tool. Two separate cohorts of infants have demonstrated that low-risk delivery characteristics (cesarean delivery without labor or prior membrane rupture, no evidence of intraamniotic infection, and no evidence of nonreassuring fetal status) confer a low risk for EOS in this population.[7,8] A third single-center study demonstrated the preliminary safety of observation for infants with respiratory distress delivered without risk factors for EOS.[22] As Flannery et al have postulated, term infants born in the setting of low-risk delivery characteristics have minimal risk of sepsis and, as such, may be considered for exemption from EOS evaluations.[8] Providers caring for this low-risk population should consider delivery mode and indication in future determinations of EOS risk. These considerations may allow for improvement in antibiotic stewardship initiatives in this specific population that has been shown to be at low risk for sepsis.

Our study has several important limitations. This is a retrospective study at a single center within the Military Health System (MHS). Within the MHS, beneficiaries have universal insurance coverage and guaranteed access to care; as such, the data presented may not be as applicable to the general population. Additionally, a few suppositions needed to be made due to the limitations of the electronic medical record. Due to inconsistent documentation of labor status or indication for delivery, we utilized ROM as a surrogate for the absence of labor. A brief ROM may not always be indicative of true absence of labor. Additionally, due to the inability to access granular vital sign data for the entire cohort, we assumed infants born via C/S without ROM, no diagnosis of maternal intraamniotic infection, no concerning birth diagnoses, and admission to the well newborn nursery would have been considered low risk by the Neonatal Early-Onset Sepsis Risk Calculator. Some of these infants, particularly those who delivered late preterm, may have been recommended by the Neonatal Early-Onset Sepsis Risk Calculator to receive a screening blood culture if "equivocal" vital sign abnormalities were present. However, that would lead our current results to actually be an underestimate of the incidence of EOS evaluations in this proven low-risk population.

Lastly, we compared the Neonatal Early-Onset Sepsis Calculator to routine clinical practice within our retrospective

cohort. Routine clinical practice during the study period was guided by categorical risk assessment. However, not all infants with respiratory distress underwent an evaluation for EOS and empiric antibiotic coverage, as would have been recommended for infants with signs of clinical illness per the categorical risk assessment algorithm.[16] This may indicate that some providers were already factoring birth indication and mode of delivery into their clinical risk assessment and choosing to observe patients with respiratory distress after delivery via C/S with ROM less than 10 minutes. If this observed subset of infants with respiratory distress had undergone evaluation and treatment per the categorical risk assessment algorithm, we may have shown a statistically significant decrease in both sepsis workup and empiric antibiotic exposure when utilizing the Neonatal Early-onset Sepsis Calculator.

Conclusion

This population of late preterm and term infants (≥35 weeks) born via C/S with ROM less than 10 minutes is at low risk for EOS, yet 19.7% underwent a laboratory evaluation for EOS using a categorical risk assessment and 14% underwent an evaluation when using the Neonatal Early-Onset Sepsis Calculator. One in seven infants would potentially be exposed to early antibiotics by both risk assessment methods. Consideration of delivery mode and indication for delivery may be beneficial to include in risk assessments for EOS.

Funding
None.

Conflict of Interest
The views expressed herein are those of the author(s) and do not necessarily reflect the official policy or position of the Defense Health Agency, Brooke Army Medical Center, the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Department of the Army, the Department of the Air Force, or the Department of Defense, nor any agencies under the U.S. Government.

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