Ensuring a Locally Tailored Response to Early Onset Sepsis Screening Meets or Exceeds the Performance of Published Approaches

Ashley Fischer, MD,† Michael Colin Mowrer, MD,* Shelly Shallat, MD,‡ Lucas Walker, MD,* Jaclyn Shallat, BS†

ABSTRACT

BACKGROUND: Evaluation of well-appearing neonates for early-onset sepsis (EOS) remains controversial. Multiple risk stratification approaches are currently used for the evaluation of EOS. Our aim was to quantify and compare frequency of laboratory evaluation and empirical antibiotics between published and local EOS approaches.

METHODS: This retrospective cohort study included 8240 infants born $\geq 35 + 0/7$ weeks' gestation at an institution from October 1, 2014, to March 1, 2018. Excluded from analysis were 156 patients who exhibited either major congenital anomalies or required antibiotics for surgical issues. A total of 1680 patient charts with risk factors for EOS were reviewed for further demographic data, clinical presentation, laboratory results, and probable recommendations from 4 EOS risk assessment approaches.

RESULTS: Laboratory evaluation recommendation was 7.1% for Centers for Disease Control and Prevention 2010 guidelines and local 2016 EOS algorithm, 6% for local 2019 EOS algorithm, and 5.9% for Kaiser Permanente neonatal EOS calculator (neonatal EOS calculator). Antibiotic recommendation was 6% for 2010 Centers for Disease Control and Prevention guidelines, 4.3% for neonatal EOS calculator, and 3.3% for local 2016 and 2019 EOS algorithms.

CONCLUSIONS: Of the 4 approaches reviewed, the local 2019 EOS algorithm and the neonatal EOS calculator were similar in recommending the lowest frequency of laboratory evaluation and the local 2016 and 2019 EOS algorithms had the lowest recommended antibiotic usage in this population.
Early-onset sepsis (EOS), defined as a blood or cerebrospinal fluid (CSF) culture obtained within 72 hours after birth growing a pathogenic bacterial species, has decreased significantly since intrapartum antibiotic prophylaxis (IAP) gained widespread use. Current incidence is ~0.5 per 1000 term and 1 per 1000 late-preterm live births. Despite decreasing incidence, term infants continue to have a 2% to 3% chance of mortality. Known risk factors for the development of EOS include preterm birth, maternal chorioamnionitis or intraamniotic infection, prolonged rupture of membranes (ROM), maternal group B Streptococcus (GBS) colonization, and inadequate IAP.

In 2010, The Centers for Disease Control and Prevention (CDC) published guidelines (2010 CDC guidelines) for infants ≥35 weeks’ gestation based on clinical appearance and known risk factors for GBS EOS. The 2010 CDC guidelines recommend antibiotic administration to all infants whose mothers are diagnosed with chorioamnionitis regardless of symptomatology, which has been controversial. Researchers have shown associations between neonatal antibiotic exposure and increased risk for asthma, alteration of neonatal microbiome, and obesity later in life. Since 2010, multiple approaches have been developed to safely reduce unnecessary antibiotic exposure for EOS. One approach is the Kaiser Permanente neonatal EOS calculator. This multivariate risk tool combines maternal risk factors with a newborn examination to guide decision-making regarding sepsis evaluation and/or antibiotic administration. An adaptation of the 2010 CDC guidelines safely reduced unnecessary antibiotics and NICU admissions by eliminating empirical antibiotics in asymptomatic newborns born to mothers with chorioamnionitis ≥35 weeks’ gestation while obtaining surveillance laboratory tests. Most recently, in the 2018 Committee of Fetus and Newborn and 2019 American Academy of Pediatrics (AAP) GBS EOS clinical reports, 3 major approaches were discussed: categorical risk assessment, multivariate risk assessment (neonatal EOS calculator), and risk assessment based on enhanced observation of newborn clinical condition.

Our aim was to quantify and compare recommended laboratory evaluation and empirical antibiotics between 4 different risk assessment approaches: 2010 CDC guidelines, neonatal EOS calculator, and locally developed laboratory surveillance 2018 and 2019 EOS algorithms.

Additionally, our goal was to review the predictive capability of each approach for cases of EOS. We hypothesized that the neonatal EOS calculator would result in the lowest laboratory and antibiotic usage and there would be no statistically significant difference in predictive capability for EOS between the 4 approaches.

METHODS

From 2010 until fall 2016, our institution used the 2010 CDC guidelines to guide clinical decision-making. In 2016, a local EOS algorithm (local 2016 EOS algorithm) adapted from the 2010 CDC guidelines was implemented (Fig 1). In the local algorithm, well-appearing infants born to mothers with chorioamnionitis are recommended to be observed with a limited diagnostic evaluation (including a blood culture at birth and complete blood cell counts (CBCs) at 12 and 36 hours of life) without empirical antibiotics. If concerning symptoms of sepsis subsequently develop or a blood culture result returns positive during the observation period, antibiotics and lumbar puncture are recommended. In alignment with the 2019 AAP GBS EOS clinical report, categorical risk assessment approach, we revised our local algorithm in 2019 (local 2019 EOS algorithm) to remove the limited sepsis workup (CBC and blood culture) from well-appearing infants born at <37 weeks and/or ROM >18 hours to mothers who received inadequate IAP.

This retrospective cohort study was performed at a midwestern urban hospital with 3000 deliveries per year and a level IV NICU. Infants born at ≥35 + 0/7 weeks’ gestation from October 1, 2014, to March 1, 2018, composed the study population. Excluded from analysis were patients with surgical conditions necessitating antibiotics or those with multiple major congenital anomalies.

Study screening criteria were applied to all eligible patients. Criteria included neonatal sepsis specific laboratories (CBC, C-reactive protein, or blood culture), antibiotics within the first 72 hours of life, maternal temperature >38°C during labor and ≤1 hour postpartum, maternal diagnosis of chorioamnionitis (as determined by obstetrician), inadequate IAP for maternal GBS colonization, and/or ROM >18 hours. Clindamycin and/or vancomycin were classified as inadequate IAP because there is insufficient clinical evidence to consider these antibiotics equivalent to B-lactam antibiotics.

A thorough chart review of the first 72 hours of life was performed for patients who met the study screening criteria. Vital signs and provider notes reflecting the first 6 hours of life were reviewed to classify the infant’s clinical presentation per the neonatal EOS calculator, 2010 CDC guidelines, and local 2016 and 2019 algorithms. For well-appearing nursery infants, vitals were performed every 30 minutes for 2 hours, hourly for hours 3 and 4, and every 4 hours for hours 4 to 24, then every 8 hours until discharge. Bedside nurses performed a head to toe assessment within 2 hours of birth whereas the initial physician examination was completed before 24 hours of life. Patients who met “clinical illness” criteria were categorized as having symptoms concerning for sepsis in all approaches. Also, patients who received antibiotics because of the development of symptoms concerning for sepsis that are not delineated in the infant classification criteria of the neonatal EOS calculator were categorized as having signs of neonatal sepsis. These symptoms include unexplained hypoglycemia, hypotonia, lethargy, and acidosis. Suggested management was determined for each of the 4 approaches: 2010 CDC guidelines, neonatal EOS calculator, local 2016, and 2019 EOS algorithms (Fig 2). The neonatal EOS calculator was accessed online from September 2017 through February 2019 for recommendations, with a presumed incidence of EOS of 0.5 per 1000 live births.
as suggested for areas with unknown incidence of EOS. The recommendation to “strongly consider empiric antibiotics” was considered equivalent to an “empiric antibiotics” recommendation.

Group differences were analyzed by using the Cochran Q test with post hoc McNemar testing. IBM SPSS Statistics version 25 (IBM SPSS Statistics, IBM Corporation) was used for statistical analysis. Statistical significance for the post hoc McNemar testing was considered a P value of < .0125. The study was reviewed and approved by the local institutional review board.

RESULTS

A total of 8240 patients were reviewed, of which 156 were excluded. Study screening criteria were applied to the remaining 8084 patients. Of these patients, 1680 infants were positive for at least one of the study screening criteria, warranting further review and analysis with the 4 EOS risk stratification approaches (Fig 2). The 6404 patients not meeting study screening criteria were not reviewed further, because the assumption was made that all 4 approaches would have neither recommended laboratory workup nor antibiotics.

Term infants, born between 37 + 0/7 weeks’ gestation and 41 + 6/7 weeks’ gestation, accounted for 90.6% of the patient population (Table 1). The average birth weight was 3344 g (2787–3901 g). A total of 52% of the patients were assigned a male sex at birth. Chorioamnionitis was diagnosed in the mothers of 207 or 2.6% of patients.

Of the 8084 patients, laboratory evaluation was recommended in 577 patients (7.1%) by the 2010 CDC guidelines and local 2016 EOS algorithm, 478 patients (5.9%) by the neonatal EOS calculator, and 484 patients (6.0%) by the local 2019 EOS algorithm (Fig 3). The neonatal EOS calculator reduced laboratories compared with the 2010 CDC guidelines and the local 2016 EOS algorithm with an absolute difference of 1.2% (95% confidence interval [CI]: 0.8–1.7), P < .001. The local 2019 EOS algorithm also reduced laboratories compared with the 2010 CDC guidelines and the local 2016 EOS algorithm with an absolute difference of 1.2% (95% CI: 0.9–1.4), P < .001. Although overall laboratory usage was lower with the neonatal EOS calculator, there were 113 patients in which the 2010 CDC guidelines did not recommend laboratories and the neonatal EOS calculator did, indicating the 2 methods are not completely overlapping in the identification of infants at risk for EOS.

Of the same 8084 patients, antibiotic administration was recommended in 484 patients (6.0%) by the 2010 CDC guidelines, 350 patients (4.3%) by the neonatal EOS calculator, and 268 patients (3.3%) by the local 2016 and 2019 EOS algorithms (Fig 4). The local 2016 and 2019 EOS algorithms reduced antibiotics compared with the neonatal EOS calculator.
with an absolute difference of 1% (95% CI: 0.8–1.3), P < .001. When compared with the 2010 CDC guidelines, the local 2016 and 2019 EOS algorithms reduced antibiotics with an absolute difference of 2.7% (95% CI: 2.3–3.0), P < .001. Similar to the laboratory findings, although the overall recommendation for antibiotics was lower with the neonatal EOS calculator, there were 48 patients in which the 2010 CDC guidelines did not recommend antibiotics but the neonatal EOS calculator did because of risk factors without a diagnosis of chorioamnionitis.

**TABLE 1** Maternal and Infant Characteristics of Newborns Admitted From October 1, 2014, to March 1, 2018

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age, n (%)</td>
<td></td>
</tr>
<tr>
<td>35 + 0/7–36 + 6/7 wk</td>
<td>743 (9.2)</td>
</tr>
<tr>
<td>37 + 0/7–38 + 6/7 wk</td>
<td>2213 (27.4)</td>
</tr>
<tr>
<td>39 + 0/7–41 + 6/7 wk</td>
<td>5108 (63.2)</td>
</tr>
<tr>
<td>42 + wk</td>
<td>20 (0.2)</td>
</tr>
<tr>
<td>Birth wt, mean ± SD, g</td>
<td>3544 ± 557</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>4174 (52)</td>
</tr>
<tr>
<td>Chorioamnionitis diagnosis, n (%)</td>
<td>207 (2.6)</td>
</tr>
<tr>
<td>Maternal temperature &gt;38°C during labor or 1 h postdelivery, n (%)</td>
<td>401 (5)</td>
</tr>
<tr>
<td>Maternal GBS inadequately treated, n (%)</td>
<td>462 (5.7)</td>
</tr>
<tr>
<td>ROM &gt;18 h, n (%)</td>
<td>509 (6.3)</td>
</tr>
</tbody>
</table>

There were 5 cases of EOS out of the 8084 patients, which translates to a local incidence of 0.62 per 1000 in our population. All patients with EOS had positive blood culture results with negative CSF culture results. The incidence of EOS in the chorioamnionitis-exposed population in this study was 1.9%. Except for 1 case of GBS, patients with EOS were born to mothers diagnosed with chorioamnionitis. The EOS cases included the following organisms: *Haemophilus influenzae*, *Enterococcus*, 2 cases of GBS, and *Streptococcus galolyticus*. Antibiotics were initiated empirically before 6 hours in all cases. The EOS calculator recommended empirical antibiotics in all cases, with the exception of *S. galolyticus*. At 41 + 0/7 weeks, the patient with *S. galolyticus* bacteremia had an ROM of 11.5 hours, a maternal temperature of 38.27°C, and maternal broad spectrum antibiotics 1 hour before delivery. This patient was classified as well-appearing by the neonatal EOS calculator, with an EOS risk of 0.53 out of 1000. Clinical judgement resulted in empirical treatment at 4.5 hours of life because of risk factors and transient neonatal temperature of 39.67°C at birth. Blood culture was obtained at birth because of our local algorithm and had a positive result at 12.5 hours. Subsequent laboratory evaluation revealed a C-reactive protein 2.79 mg/dL, white blood cell count 44 000, an immature to total neutrophil ratio 0.3, and procalcitonin 61.66 ng/mL. Postantibiotic lumbar puncture resulted in a negative culture result with an elevated CSF white blood cell count. A pediatric infectious disease specialist advised the diagnosis of EOS and recommended treatment of culture-negative meningitis.

**DISCUSSION**

There are 3 described approaches to EOS risk stratification in infants born ≥35 weeks’ gestation: categorical risk assessment, multivariate risk assessment, and risk assessment based on newborn clinical condition. Categorical risk assessments do not take into account clinical appearance for chorioamnionitis-exposed infants, such as the 2010 CDC guidelines, are limited by the empirical treatment of many low-risk newborns. Multivariate risk assessments, such as the neonatal EOS calculator, are an effective approach for decreasing antibiotic and laboratory usage in low-risk newborns by incorporating clinical illness into risk stratification and providing objective criteria for defining clinical illness. Although physician subjectivity is often a limitation, relying on objective criteria more heavily than physician clinical judgement could increase unnecessary evaluation and/or treatment of otherwise low-risk patients with confounding alternative diagnoses.
example, patient symptoms that are consistent with noninfectious disease processes, such as transient tachypnea of the newborn, respiratory distress syndrome, or environmental or transitional temperature instability in a late-preterm or small for gestational age infant, could result in the recommendation of laboratory evaluation and possible antibiotic treatment when using the objective neonatal EOS calculator without due attention to clinical judgement. Alternatively, some centers have demonstrated advantages of enhanced clinical observation alone regardless of the presence of risk factors in an asymptomatic patient. With this in mind, the AAP recommends that each institution develop their own approach to EOS risk stratification based on local practices, resources, and EOS incidence.

For the purposes of this study, we investigated the predictive ability of 4 different approaches during the first 6 hours of life using actual patient data and reviewing the respective ability to predict EOS cases. We identified and reviewed all EOS cases and gathered data on how each algorithm performed in recommending laboratory evaluation and empirical antibiotics. The significance of the case of S gallolyticus is unknown, as the patient was asymptomatic at the time of diagnosis. Because of the retrospective nature of the study, it is difficult to discern if this patient was identified and treated before the onset of clinical symptoms or was in fact unnecessarily diagnosed with and treated for EOS. Review of significantly more EOS cases would be necessary to draw valid conclusions on approach predictive capability for EOS.

Because of the large number of patients at risk for EOS that were reviewed, we were able to draw significant conclusions regarding approach recommendations for laboratory evaluation and empirical antibiotics. Of the 4 approaches reviewed, the local 2019 EOS algorithm and the neonatal EOS calculator were similar in laboratory evaluation, and the local 2016 and 2019 EOS algorithms had the lowest recommended antibiotic usage.

Of note, the results likely underestimated the laboratory and antibiotic recommendation of the neonatal EOS calculator because of our initial study screening criteria. Oxygen requirement, respiratory distress, and abnormal vital signs were not included in our screening criteria. When using the neonatal EOS calculator, a criteria for clinical illness categorization is the persistent need for nasal continuous positive airway pressure, high flow nasal cannula, mechanical ventilation (outside of the delivery room), or the need for supplemental oxygen ≥2 hours to maintain oxygen saturations >90% (outside of the delivery room). In our institution, we do not automatically initiate laboratory workup nor antibiotic administration to patients with oxygen requirements in the absence of infectious risk factors if an alternative diagnosis is strongly suspected. For example, a patient without concern for chorioamnionitis exposure requiring 4 hours of high flow nasal cannula support after a repeat cesarean delivery with ROM at delivery would not necessarily receive laboratories or antibiotics. With a neonatal EOS calculator clinical illness presentation, the
risk stratification for EOS is significantly increased and ubiquitously carries an empirical or strongly consider starting empirical antibiotics recommendation. There is a future Cochrane Review planned to evaluate the utility of antibiotics for the management of transient tachypnea of the newborn.18

Additionally, the study screening criteria did not include abnormal neonatal vital signs or respiratory distress. With the neonatal EOS calculator, abnormalities in vital signs or respiratory distress alone can result in an “equivocal” presentation classification, which, although to a lesser extent than the clinical illness presentation, increases the calculated risk of sepsis. Although a patient may not meet the threshold for evaluation or treatment by prenatal risk factors or equivocal presentation alone, possession of either or both may result in interventions because of the nature of the multivariate risk assessment tool. For example, the neonatal EOS calculator recommends laboratories for a well-appearing 35 + 0/7 week infant with a ROM of 17 hours whose mother is negative for GBS and has a temperature of 37.95°C. Depending on the persistence of the abnormal vital sign, a temperature of <36.39°C and/or a respiratory rate >60 breaths per minute could result in an equivocal presentation and subsequently the recommendation for antibiotics. With the methods of our study, this patient would not have met study screening criteria and therefore would not have met criteria for further review.

Also, we used the CDC EOS incidence of 0.5 per 1000 when accessing the neonatal EOS calculator as our local incidence was unknown.14 We subsequently recognized our local EOS incidence to be 0.62 per 1000. Had we entered the higher EOS incidence into the neonatal EOS calculator, additional interventions would likely have been recommended. In regard to the case of S. galolyticus EOS, entering an incidence of 0.7 per 1000 into the neonatal EOS calculator would not have changed intervention recommendations.

Interestingly, many of the published retrospective studies analyzing the neonatal EOS calculator only include patients whose mothers were diagnosed with chorioamnionitis.19–21 As found in a recent meta-analysis,22 including only chorioamnionitis-exposed infants may overestimate the advantages of the neonatal EOS calculator. Additionally, researchers of previously published studies used the 2010 CDC guidelines or similar versions recommending empirical antibiotic and laboratory evaluation for all chorioamnionitis-exposed neonates as the conventional management strategy for comparison.23 To our knowledge, this is the first publication in which researchers compare the neonatal EOS calculator to an alternative management strategy that limits antibiotic usage for chorioamnionitis-exposed neonates while including infants at risk for EOS due to risk factors other than chorioamnionitis exposure.

This study was limited by its retrospective nature. The subjectivity of interpreting and defining signs of clinical illness or neonatal sepsis and variability in provider practice further limited this study. Although evaluation of the effectiveness of the local 2019 EOS algorithm’s ability to predict EOS was described in this article, the impact on readmissions for sepsis after our process change needs quantification and is currently being evaluated.

All studied methods appeared to be similar in safety. Although not statistically significant, 1 case of EOS may have been identified with surveillance culture as opposed to observation recommendations from the neonatal EOS calculator. Because this was an atypical bacterial species in an asymptomatic patient, its significance is difficult to discern. We are also unable to determine if the surveillance laboratories in combination with clinical observation was truly advantageous to clinical observation alone in this retrospective study. The 2019 AAP GBS EOS clinical report recommends birth centers develop locally tailored, documented guidelines for EOS risk assessment and clinical management.14 We therefore conclude that in this clinical setting, tailoring the 2010 CDC guidelines to eliminate antibiotic administration for well-appearing patients exposed to maternal chorioamnionitis and eliminating laboratory workup for well-appearing patients with inadequately treated maternal GBS is a reasonable alternative approach to the neonatal EOS calculator in reducing unnecessary laboratories and antibiotics.

Acknowledgments
We thank Karen Fenelon for her assistance in data extraction.

REFERENCES
1. 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;142(6):e20182894


