Early onset sepsis risk calculator: Application in an outer metropolitan hospital

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SUMMARY
Neonatal early onset sepsis (EOS) is potentially life-threatening. EOScalc is an evidence-based tool developed in California in 2016 to guide management decisions for newborns suspected of EOS. This retrospective study at an outer metropolitan hospital in Melbourne compared EOScalc clinical recommendations based on EOS predictors and the infant’s clinical presentation with actual treatment decided upon and administered by treating clinicians. We found that the EOScalc would result in a number of potential benefits, including a reduction in the number of neonatal investigations performed, a reduction in neonatal antibiotic administration, and decreased separation of newborns from their mothers.

Key Words
Neonatal early-onset sepsis, sepsis, paediatrics, antibiotics

ABSTRACT
Background
Neonatal early onset sepsis (EOS) is potentially life-threatening. EOScalc is an evidence-based tool developed in California in 2016 to guide management decisions for newborns suspected of EOS.

Aims
The aim of this study was to determine whether management decisions guided by the EOScalc could reduce the number of newborns admitted to the special care nursery (SCN) for empiric antibiotic administration compared with clinician-driven management decisions at an outer metropolitan hospital in Melbourne.

Method
We performed a retrospective medical record review over a three-month period on mother-baby pairs where newborns ≥34 weeks’ gestation with presumed EOS were treated with empiric antibiotics. We entered EOS predictors into the EOScalc for each newborn and compared the clinical recommendations based on the infant’s clinical presentation with actual treatment decided upon and administered by treating clinicians.

Conclusion
Use of the EOScalc would result in several potential benefits, including a reduction in the
number of neonatal investigations performed, a reduction in neonatal antibiotic administration, and decreased separation of newborns from their mothers.

**BACKGROUND**

Neonatal sepsis affects 2,202 per 100,000 live births. It is a serious condition, more common in newborns born prematurely, and has a mortality rate of 11–19 per cent.\(^1\) Neonatal sepsis is commonly classified as either “early” (symptom onset within 48 hours of life) or “late” (symptom onset >48 hours of life).\(^2\) Early onset sepsis (EOS) occurs mainly through vertical transmission, from mother to newborn, after rupture of membranes or during labour, with the most common causative bacteria being *Group B Streptococcus* (GBS) and *Escherichia coli*.\(^2\)–\(^4\) Since the introduction of routine antepartum GBS screening and prophylactic intrapartum antibiotic administration, the EOS rate has decreased worldwide.\(^3\)–\(^5\) Despite these preventative measures, EOS has been reported to still occur in 0.01–0.83 per 1,000 infants in Western countries.\(^4\)–\(^6\) The management of potential EOS is conservative, largely due to diagnostic challenges, including non-specific presenting signs and the delay in definitive diagnosis with a positive blood or cerebrospinal fluid (CSF) culture identifying the causative organism.\(^7\)–\(^9\) This cautious approach results in 8–15 per cent of all newborns still being admitted to a special care nursery (SCN) or neonatal intensive care unit (NICU) for suspected EOS investigation and urgent antibiotic administration, despite the low incidence of proven EOS.\(^4\)–\(^6\)

Current EOS management is generally specified by local and international guidelines, such as the National Institute for Health and Care Excellence in the United Kingdom, the Centres for Disease Control and Prevention in Australia, and state-based or hospital guidelines, coupled with clinical expertise.\(^5\)–\(^10\) When EOS is suspected, standard management typically involves blood investigations, including monitoring of inflammatory markers, such as C-reactive protein (CRP) and white cell count (WCC), which have poor predictive values for EOS when used alone,\(^11\) and sending blood cultures prior to commencing empiric antibiotics. It is thought that current guidelines result in potentially higher than necessary empiric antibiotic administration.\(^5\)–\(^10\)

Therefore, an evidence-based EOS risk stratification tool (EOScalc) for neonates ≥34 weeks’ gestation was developed in California in 2016. The EOScalc considers the hospital’s incidence of neonatal sepsis, maternal clinical and intrapartum predictors (Table 1) for EOS, and newborn gestational age and time-dependent clinical status.\(^12\) The EOScalc provides clinicians with one of four management pathways (Table 2) based on consensus clinician opinion.\(^3\)–\(^7\),\(^10\)

The EOScalc tool has been studied and implemented by multiple health networks within Australia; however, at the time of writing this article, there has been no published data regarding the benefits of applying the EOScalc at an outer metropolitan hospital in Melbourne. Therefore, the aim of this study was to determine whether management decisions guided by the EOScalc could reduce the number of newborns admitted to the hospital SCN for empiric antibiotic administration, compared with clinician-driven management decisions.
Table 1: Early onset sepsis predictors included in the early onset sepsis risk stratification tool

<table>
<thead>
<tr>
<th>Early onset sepsis predictor (value)</th>
<th>Risk of EOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age of newborn (weeks and days)</td>
<td>Risk decreases from 34 to 40 weeks’ gestation and rises again after 40 weeks’ gestation</td>
</tr>
<tr>
<td>Highest recorded maternal antepartum temperature (degrees Celsius)</td>
<td>Maternal fever (&gt; 38°C) increases risk</td>
</tr>
<tr>
<td>Time from membrane rupture (ROM) to delivery of infant (h)</td>
<td>ROM ≥18 h increases risk</td>
</tr>
<tr>
<td>Maternal GBS status (positive, negative, unknown)</td>
<td>Positive GBS increases risk</td>
</tr>
<tr>
<td>Maternal intrapartum antibiotics administered</td>
<td>Intrapartum antibiotic exposure (of any type and duration), compared with no antibiotic exposure, is associated with a two-fold increase in infection. Any intrapartum antibiotic given &gt;4 hours before delivery associated with a decreased risk of infection.</td>
</tr>
</tbody>
</table>

Abbreviations: GBS=Group B Streptococcus, h=hours, EOS=Early onset sepsis

Table 2: Early onset sepsis calculator (EOScalc) management recommendations based on EOS predictors and newborn clinical exam classification

The four EOScalc management recommendation groups

1. Routine postnatal ward care
2. Blood culture and enhanced observations (four hourly for 24 hours)
3. Blood culture and consider empiric antibiotics based on clinical presentation
4. Blood culture and administer empiric antibiotics

1Blood culture for newborns with an EOS risk of at least 1 per 1000 live births.7
2Empiric antibiotics for newborns with an EOS risk of 3 or more per 1000 live births.7

METHOD
We performed a retrospective, observational case review study in newborns ≥34 weeks’ gestation treated for presumed EOS (administered antibiotics < 48 hours of life) at the hospital between 1 July 2019 and 30 September 2019. The EOScalc was not routinely used to guide management for antibiotic prescription during the study period. We defined confirmed EOS as bacteraemia or bacterial meningitis with a positive blood or CSF culture and symptom onset within 48 hours of birth.5

We collected maternal and newborn data from medical records (Table 3). We determined the median number of hours from birth to antibiotic administration and duration of administration. We entered EOS predictors (Table 1) into the EOScalc to compute the prior probability of EOS per 1,000 live births.13 We used an EOS incidence of 0.6 per 1,000 newborns in the EOScalc.
Based on documented clinical exam findings within the first 48 hours of life, each newborn was categorised into one of the three clinical exam classifications; well appearing, equivocal, or clinical illness (Table 4), defined by the EOScalc. We computed an EOScalc risk corresponding to one of four clinical management recommendations (Table 2) for each newborn. We compared the EOScalc management recommendation with clinician-derived treatment administered for each newborn. The “administer antibiotics” and “consider antibiotics” recommendation groups were combined and deemed to be the same treatment as what the newborns received within this study period—ie, “administer antibiotics”. We analysed the results in Microsoft Excel (Version 2007).

<table>
<thead>
<tr>
<th>Newborn Data</th>
<th>Maternal Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date and time of birth</td>
<td>Labour type: normal vaginal delivery or caesarean</td>
</tr>
<tr>
<td>Gestational age</td>
<td>Antepartum temperature (degrees Celsius)</td>
</tr>
<tr>
<td>Gender</td>
<td>Time of membrane rupture</td>
</tr>
<tr>
<td>Clinical symptoms &lt;48 hours</td>
<td>GBS status (positive, negative, unknown)</td>
</tr>
<tr>
<td>Blood and cerebrospinal fluid culture result</td>
<td>Intrapartum antibiotics type and time administered</td>
</tr>
<tr>
<td>Antibiotics: type, time administered and duration</td>
<td>SCN admission indication¹</td>
</tr>
<tr>
<td>SCN admission indication¹</td>
<td>SCN length of stay</td>
</tr>
</tbody>
</table>

Abbreviations: SCN=Special care nursery; EOS=Early onset sepsis; GBS=Group B Streptococcus

¹As recorded in SCN discharge summary.

RESULTS

There were 961 live births at the hospital between 1 July 2019 and 30 September 2019. During this period, forty-six (0.05 per cent) newborns (26 males, 20 females) ≥34 weeks’ gestation were investigated and treated in the hospital SCN for suspected EOS. Forty-three mother–newborn pairs (25 males, 18 females) had complete data available for the EOScalc (Figure 1), and we included them in the analysis. Most newborns (25) were delivered via caesarean; 18 were delivered via normal vaginal delivery. The mean gestational age of newborns was 38 weeks (range: 34 weeks 1 day–41 weeks 3 days) with 17 born prematurely (34 weeks–36 weeks 6 days). The median SCN admission length was four days (range: 2–19 days).

The median number of hours from birth to antibiotic administration was 1.7 hours (range: 0.7–49.9 hours). All newborns received empiric antibiotics as per local guidelines, ie, penicillin and gentamicin, for a median of 19.5 hours (range: 0–132 hours) and 11.5 hours (range: 0–62.5 hours), respectively. One newborn also received Cefotaxime for treatment of suspected meningitis as per local empiric antibiotic guidelines.

Thirteen newborns were classified as “clinically ill”, 13 “equivocal”, and 17 “well appearing” (Figure 2) based on the documented clinical signs present within the first 48 hours of life using the EOScalc clinical exam classification criteria (Table 4). Three newborns were asymptomatic according to medical records.
Table 4: Classification of newborns’ clinical presentation in the EOScalc

<table>
<thead>
<tr>
<th>Clinical Exam Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Illness</strong></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Persistent need for NCPAP/HFNC/mechanical ventilation (outside of the delivery room)</td>
</tr>
<tr>
<td>2.</td>
<td>Hemodynamic instability requiring vasoactive drugs</td>
</tr>
<tr>
<td>3.</td>
<td>Neonatal encephalopathy/Perinatal depression</td>
</tr>
<tr>
<td></td>
<td>- Seizure</td>
</tr>
<tr>
<td></td>
<td>- Apgar Score @ 5 minutes &lt; 5</td>
</tr>
<tr>
<td>4.</td>
<td>Need for supplemental O₂ &gt; 2 hours to maintain oxygen saturations &gt; 90% (outside of the delivery room)</td>
</tr>
<tr>
<td><strong>Equivocal</strong></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Persistent physiologic abnormality &gt; 4 hrs</td>
</tr>
<tr>
<td></td>
<td>- Tachycardia (HR &gt; 160)</td>
</tr>
<tr>
<td></td>
<td>- Tachypnoea (RR &gt; 60)</td>
</tr>
<tr>
<td></td>
<td>- Temperature instability (&gt; 38°C or &lt; 36.4°C)</td>
</tr>
<tr>
<td></td>
<td>- Respiratory distress (grunting, flaring, or retracting) not requiring supplemental O₂</td>
</tr>
<tr>
<td>2.</td>
<td>Two or more physiologic abnormalities lasting for &gt; 2 hrs</td>
</tr>
<tr>
<td></td>
<td>- Tachycardia (HR &gt; 160)</td>
</tr>
<tr>
<td></td>
<td>- Tachypnoea (RR &gt; 60)</td>
</tr>
<tr>
<td></td>
<td>- Temperature instability (&gt; 38°C or &lt; 36.4°C)</td>
</tr>
<tr>
<td></td>
<td>- Respiratory distress (grunting, flaring, or retracting) not requiring supplemental O₂</td>
</tr>
<tr>
<td><strong>Well Appearing</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No persistent physiologic abnormalities</td>
</tr>
</tbody>
</table>

Note: Abnormality can be intermittent.

Abbreviations: NCPAP=Nasal continuous positive airway pressure; HFNC=High flow nasal cannula; O₂=oxygen; HR=Heart rate; RR=Respiratory rate; °C=degrees Celsius

Compared with clinician-derived management in which 43 newborns had blood cultures collected and empiric antibiotics administered in the hospital SCN, the EOScalc recommended that 21 newborns receive no additional care, three have blood cultured and undergo increased observations (four hourly for 24 hours), nine have blood cultured and consider antibiotics pending clinical picture, and 10 have blood cultured and commence antibiotics immediately (Figure 3). Nineteen newborns were deemed to have the same care recommended by the EOScalc as they received (blood culture and empiric antibiotics). Twenty-nine newborns had at least one EOS predictor present (Figure 4); of these, 15 were recommended by the EOScalc to receive “no additional care”.

There were no positive bacterial cultures reported from the blood (43 newborns) and CSF (2 newborns) specimens collected, and there were no deaths due to sepsis or any other cause reported in the following two months.
Despite its small sample size, this study shows that the EOScalc recommends fewer newborns receive empiric antibiotics for the management of suspected EOS compared with current antibiotic prescribing practices by paediatric clinicians at the hospital. These findings are consistent with studies conducted in Australia and other Western countries.\textsuperscript{3,5,6,10} The EOScalc recommended that 19 of the newborns investigated and treated for suspected EOS undergo the same treatment. Meanwhile, the EOScalc recommended that 21 continue with standard post-natal ward care, receiving no further investigation or empiric antibiotics at the time of clinical assessment.

Identifying newborns with EOS using all current risk-based screening tools is difficult.\textsuperscript{5} It is much easier to identify patients at risk of EOS who are symptomatic and justify antibiotic use compared with those who appear well or only have minor physiological disturbances,\textsuperscript{12} particularly as 50 per cent of newborns with EOS have no symptoms at birth.\textsuperscript{7} Therefore, it is common that asymptomatic newborns are still treated for suspected EOS, as found in our study, especially when risk factors are present.\textsuperscript{14} Given the potentially serious adverse consequences of not treating a newborn with suspected EOS,\textsuperscript{11} there is a balance between overtreating low-risk infants and missing potentially asymptomatic septic neonates.

We found the median time to antibiotic administration in our patient cohort was under two hours, with only 18 of the 43 newborns commencing antibiotics after two hours of life. This suggests that even though it is known that most newborns will become “well appearing” by two hours of life,\textsuperscript{1} it is challenging for treating clinicians to withhold investigation and treatment for suspected EOS. However, the publishers of the EOScalc propose that the reduction in unnecessary antibiotic administration outweighs any consequences of possible “delayed” antibiotic administration.\textsuperscript{16}

Although a positive blood culture confirms a diagnosis of suspected sepsis, between 30–75 per cent of children with clinical features of sepsis yield no growth on blood cultures.\textsuperscript{8,9} One explanation for this may be due to inadequate blood volume collection for reliable culture results, secondary to clinician concern about repeated phlebotomies and associated pain and infection risk.\textsuperscript{8,10} In symptomatic neonates, a negative culture result is often treated with scepticism,\textsuperscript{8} with decisions to continue suspected EOS treatment often guided by clinical response to treatment and other markers of infection.\textsuperscript{11}

A more conservative approach and lower threshold for investigation and treatment in non-tertiary facilities is justifiable. To ensure this conservative approach continues if the EOScalc was to be implemented into clinical practice, a higher incidence of EOS can be incorporated, as we did in this study. By providing one of four management recommendations, the EOScalc is able to highlight newborns at higher risk of EOS. Increased training of staff and education of parents may be beneficial for identifying those higher-risk newborns who may quickly progress from well-appearing to symptomatic.\textsuperscript{5,10,11} This increased vigilance and training has been found to use fewer
resources than is required for unnecessary SCN admission and antibiotic administration, improving patient flow and reducing time to discharge. However, in a culturally and linguistically diverse patient population, such as at this hospital, reliance on newborn families to identify and communicate a change in newborn clinical status may prove more challenging compared with a patient population that mainly speaks English as a first language and may have a higher level of health literacy.

Management of suspected EOS, whether proven by blood culture or not, impacts on both newborns and their parents. Investigation procedures are painful, and treating suspected EOS means newborns are separated from their mothers, which is linked with late initiation of breastfeeding and increased formula supplementation. Furthermore, neonatal antibiotic administration may influence the composition of the infant gut microbiome, predisposing it to necrotising enterocolitis in the extremely premature population. Other conditions that have been hypothesised to be associated with early-life antibiotic use include asthma, inflammatory bowel disease, and autoimmune diseases. Research is ongoing into the potential negative consequences of neonatal antibiotic administration.

Studies conducted in developed countries worldwide suggest that the EOScalc tool is both safe and effective, with implementation associated with numerous positive outcomes without increasing mortality. These outcomes include a reduction in empiric antibiotic therapy use in the first 24 hours from 5.0% to 2.6% (adjusted difference, −1.8%; 95% CI, −2.4% to −1.3%) following implementation of the EOScalc, fewer laboratory tests (reduced from 14.5% to 4.9%; adjusted difference, −7.7%; 95% CI, −13.1% to −2.4%), and fewer admissions to SCN and NICU (93% reduction from baseline). Furthermore, the EOScalc reduces the number of newborns separated from their family, increases exclusive breastfeeding rates (from less than 10% to over 50%) and improves maternal-newborn bonding. Although we did not assess safety, our study supports these findings.

In addition to potential health and relationship benefits, the EOScalc has been shown to have healthcare cost benefits in developed countries. Savings resulted from cost reductions in the management of sepsis and direct and indirect costs for long-term disability. Given newborns suspected of EOS at this outer metropolitan hospital in Melbourne are admitted to SCN to undergo investigation and receive empiric antibiotic therapy, and that the EOScalc recommended fewer patients be investigated and treated for suspected EOS, it is reasonable to assume that there would be an economic benefit for the hospital and state government if the EOScalc was implemented as part of clinical practice. However, we did not explore the cost benefits in our study.

Strengths of this study include the comparison of current clinician decisions versus EOScalc recommendations for suspected EOS management in an outer metropolitan hospital in Melbourne. Even with a small cohort, it is the first step in understanding whether the EOScalc is a suitable tool to be implemented into clinical practice at health networks with a similar patient population.
The study has several limitations. Due to it being a retrospective case review study, the findings are limited by the accuracy of the data. Therefore, caution must be taken when comparing the decisions made during the study period and management recommendations by the EOScalc. Further, we only reviewed newborns who had antibiotics documented in medication charts. We did not analyse what the EOScalc would have recommended for those newborns who did not receive antibiotics. An understanding of patient and clinician factors influencing treatment decisions and clinician acceptance of the EOScalc recommendations is necessary and will ensure smooth implementation of the EOScalc into clinical workflow.

CONCLUSION
Our analysis demonstrated that the EOScalc potentially reduces antibiotic administration and subsequent unnecessary separation of newborns from mothers and neonatal investigations in an outer metropolitan hospital patient population, such as the hospital in this study. The EOScalc can assist decision-making and aid antibiotic stewardship by reducing unnecessary antibiotic use. Coupled with clinical expertise, the EOScalc allows an individualised care approach for suspected EOS, with benefits for both the newborn and family.

REFERENCES


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CONFLICTS OF INTEREST
The authors declare that they have no competing interests.

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None

ETHICS COMMITTEE APPROVAL
The study was approved by the Human Research Ethics Committee at Werribee Mercy Hospital (Project: 2020-023).
Figure 1: EOS predictors collected from patient data (n=43) and entered into the EOS risk stratification tool

Abbreviations: GBS = Group B Streptococcus; EOScalc = early onset sepsis risk calculator; h = hours; w = weeks; d = days

1Highest recorded intrapartum temperature
Figure 2: EOS risk stratification tool clinical exam classification for newborns (n=43) who were investigated and treated for suspected EOS at the hospital

Abbreviations: EOS=early onset sepsis; EOScalc=early onset risk sepsis calculator
Figure 3: EOS risk stratification tool recommended management for newborns (n=43) investigated and treated for suspected EOS at the hospital

Abbreviations: EOS=early onset sepsis; EOScalc=early onset sepsis risk calculator

1Treatment received for suspected EOS between 1 July 2019 and 30 September 2019 at the hospital included newborn admitted to special care nursery, blood cultures obtained and administered empiric antibiotics.

2EOScalc recommended management is determined by the EOS risk factors present and clinical exam of the newborn.
Figure 4: EOS predictors and EOScalc recommendations for the newborns (n=43) investigated and treated for EOS at the hospital

Abbreviations: EOS=early onset sepsis; EOScalc=early onset sepsis risk calculator

1At least one EOS predictor: rupture of membranes > 18 hours, gestational age < 37 weeks, febrile (>28 °Celsius), positive GBS status, maternal intrapartum antibiotics administered < 4 hours before delivery.
2Four hourly observations for 24 hours
3Based on clinical exam