The Neonatal Early-Onset Sepsis Calculator and Its Impact at a Single Center: A Retrospective Cohort Study

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Abstract

Objective: *To determine whether usage of the Neonatal Early-Onset Sepsis (EOS) Calculator decreases sepsis evaluations, antibiotic administration, length of stay (LOS), and resource utilization when caring for newborns whose mothers were diagnosed with confirmed chorioamnionitis (CAM).*

Study Design: *This retrospective cohort study enrolled 236 dyads of mothers and newborns (≥ 35 weeks gestation). De-identified data, including newborn antibiotic usage, complete blood counts (CBC), blood cultures, and LOS, were collected one year before and after the 2019 implementation of the EOS calculator. To summarize the data for all study variables, descriptive statistics were utilized. All categorical variables were compared using the Fisher exact or* $\chi 2$ *test, and the Wilcoxon Rank Sum test was applied for continuous variables.*

Results: *A significant reduction was seen in the incidence of sepsis evaluations (*$P < 0.001$*) and antibiotic use (*$P < 0.001$*) after the implementation of the EOS calculator. An Arizona Medicare reimbursement rate estimation revealed that the median expense of EOS-related care decreased by $257.89 in infants whose mothers were diagnosed with confirmed CAM (*$P < 0.0001$*).*

Conclusion: *The frequency of sepsis evaluations and antibiotic utilization in newborns of mothers diagnosed with confirmed CAM was significantly reduced with the use of the EOS calculator, resulting in decreased resource utilization.*

Keywords: Newborn, Infant, Neonatal Sepsis, Blood Cell Count, Reimbursement Rates, Chorioamnionitis, Blood Culture, Length of Stay, Anti-bacterial Agents

"Early onset sepsis (EOS) is a severe neonatal condition occurring within the first 72 hours of life, and its certain diagnosis can be difficult. (1) The vague symptoms can include poor feeding, hypoglycemia, respiratory distress, and apnea."

Introduction

Early onset sepsis (EOS) is a severe neonatal condition occurring within the first 72 hours of life, and its certain diagnosis can be difficult. (1) The vague symptoms can include poor feeding, hypoglycemia, respiratory distress, and apnea. Among upper-income countries, the United States has the highest neonatal mortality rates (4/1000 live births). (2) Sepsis is a predominant contributing factor to neonatal morbidity and mortality. (3,4) Often, chorioamnionitis (CAM), the acute inflammation of amniotic/chorionic membranes, and the fluid surrounding the fetus during pregnancy cause EOS. (5) The presence of one or more of the following maternal risk factors; Group B *Streptococcus* (GBS) colonization, fever (temperature > 38.0 C), and prolonged rupture of membranes (≥ 18 hours) may also result in CAM. (3,6-8)

"Several risk stratification schemes for EOS are recommended by the American Academy of Pediatrics (AAP). The Kaiser Permanente Neonatal EOS Calculator(9) uses its multivariate approach to assess maternal risk factors and the infant's clinical presentation. (10) "

Several risk stratification schemes for EOS are recommended by the American Academy of Pediatrics (AAP). The Kaiser Permanente Neonatal EOS Calculator(9) uses its multivariate approach to assess maternal risk factors and the infant's clinical presentation. (10) Some institutions report the screening and treatment of up to 15% of all newborns for EOS despite the true low incidence at 0.5-1.2 per 1,000 live births. (1) The methods used to screen for sepsis have been extensively evaluated, and the complete blood count (CBC) components are proven to be neither very sensitive nor specific for EOS. (4,11,12) Blood cultures are reliable only when the volume of blood collected is adequate for analysis. Schelonka et al. (13) found it is necessary to have a minimum of 1 to 2 milliliters (mL) of blood collected to detect less than four colony-forming units /mL to ensure sepsis is detected. Up to 60% of cultures will be falsely negative if only a half mL of blood is collected. (13) Additionally, it may take 24 hours or longer for results to return from the laboratory making the timely and accurate diagnosis of EOS difficult. (14) All of these factors may ultimately lead to practitioners prescribing antibiotic therapy in the newborn without the presence of a truly positive blood culture. (3,6)

There are many types of adverse effects associated with early antibiotic administration. A correlation between the development of resistant bacteria and antibiotic overuse has been identified. (3) Antibiotics alter the intestinal microbiome and can be linked to inflammatory bowel disease, obesity, and respiratory disorders later in childhood. (15-17) Also, infants who need intravenous antibiotic administration will likely be cared for in the nursery, thus separated from their mothers for prolonged periods. This may affect the initiation and/or maintenance of breastfeeding and, ultimately,

Table 1 Demographic Characteristics

	Pre (n=111)	Post (n=125)	*P*-value
Gestational age (weeks)(a)	39 (38-40)	39 (39-40)	0.997
Birth Weight (grams)(a)	3400 (3090-3680)	3440 (3210-3610)	0.503
Race (b)			0.875
American Indian	2 (2)	4 (3)	
Black	11 (10)	13 (10)	
Other/Unknown	6 (5)	5 (4)	
White	92 (83)	103 (83)	
Ethnicity (b)			0.057
Hispanic	61 (55)	63 (50)	

(a) Median (Interquartile Range); (b) n (Percentage)

bonding. (5) For the above reasons, a practitioner must be judicious when prescribing antibiotics for infants with negative blood cultures. (3)

"Recent prospective studies have shown that using an EOS calculator can safely decrease the need for empiric antibiotic treatment, laboratory tests, and unnecessary nursery admissions, which may ultimately decrease the length of stay (LOS) and costs.(1,5,15)"

A uniform treatment plan of EOS for the term and near-term infants whose mothers were diagnosed with CAM was lacking in clinical practice. The Neonatal Early-Onset Sepsis Calculator was created by Kaiser Permanente, which guides medical management by measuring maternal risk factors and reviewing their newborn's clinical presentation. (10)The non-subjective tool was developed to minimize unnecessary interventions. In 2018, the AAP's Committee on Fetus and Newborn published a report supporting the use of Kaiser Permanente's EOS Calculator as an acceptable approach to manage suspected or proven bacterial sepsis in infants > 35 weeks of age. (10) Recent prospective studies have shown that using an EOS calculator can safely decrease the need for empiric antibiotic treatment, laboratory tests, and unnecessary nursery admissions, which may ultimately decrease the length of stay (LOS) and costs.(1,5,15)

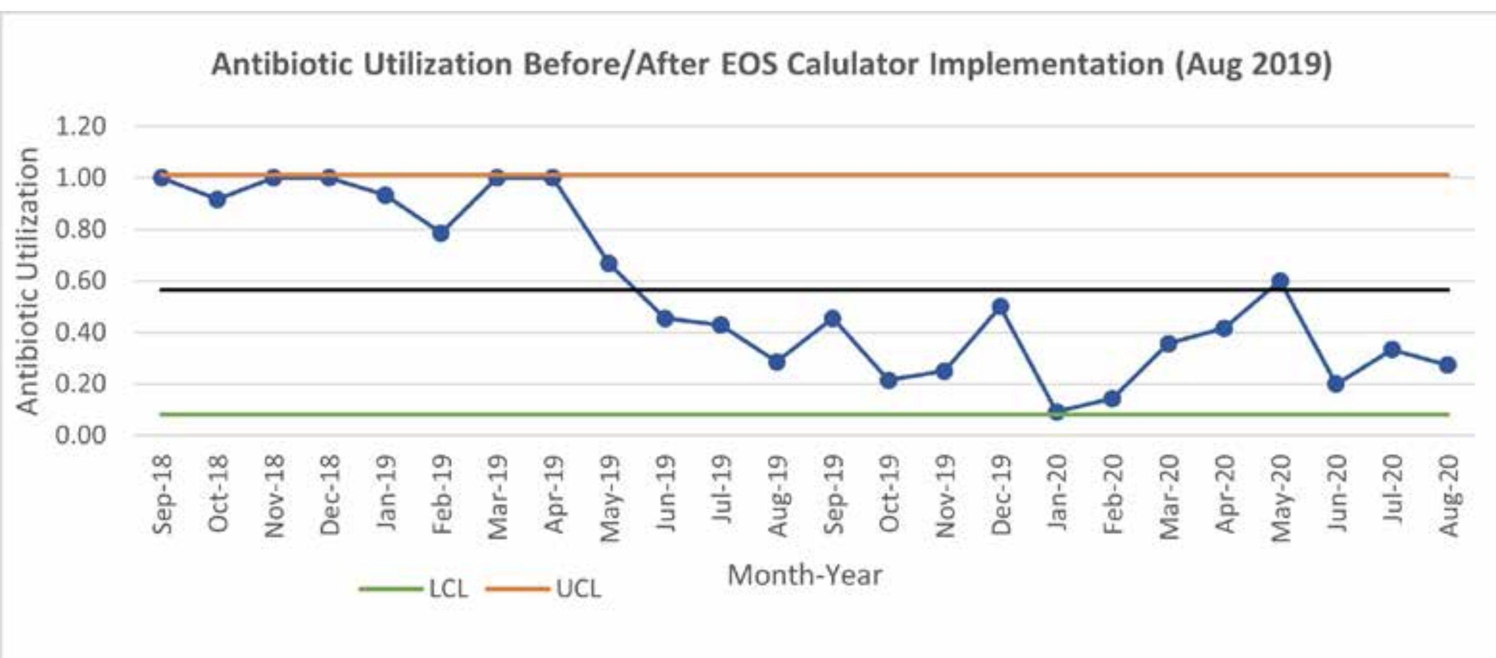


Table 2 EOS Healthcare Utilization and Associated Costs per Newborn

	Pre (n=111)	Post (n=125)	*P*-value
EOS Healthcare Utilization			
Laboratory Tests (a)	97 (87)	81 (65)	**<0.001**
Empiric Antibiotic Courses(a)	89 (80)	40 (32)	**<0.001**
Antibiotic Days (b)	2 (2-3)	0 (0-2)	**<0.0001**
Length of Stay in Days (b)	2.3 (2.1-2.6)	2.3 (2.0-2.7)	0.875
EOS Costs (b)			
Laboratory Tests	$34.34 (34.34-34.34)	$34.34 (0-34.34)	**<0.0001**
Antibiotic Treatment	$257.89 (257.89-257.89)	$0 (0-257.89)	**<0.0001**
Combined (Tests & Antibiotics)	$292.23 (292.23-292.23)	$34.34 (0-292.53)	**<0.0001**

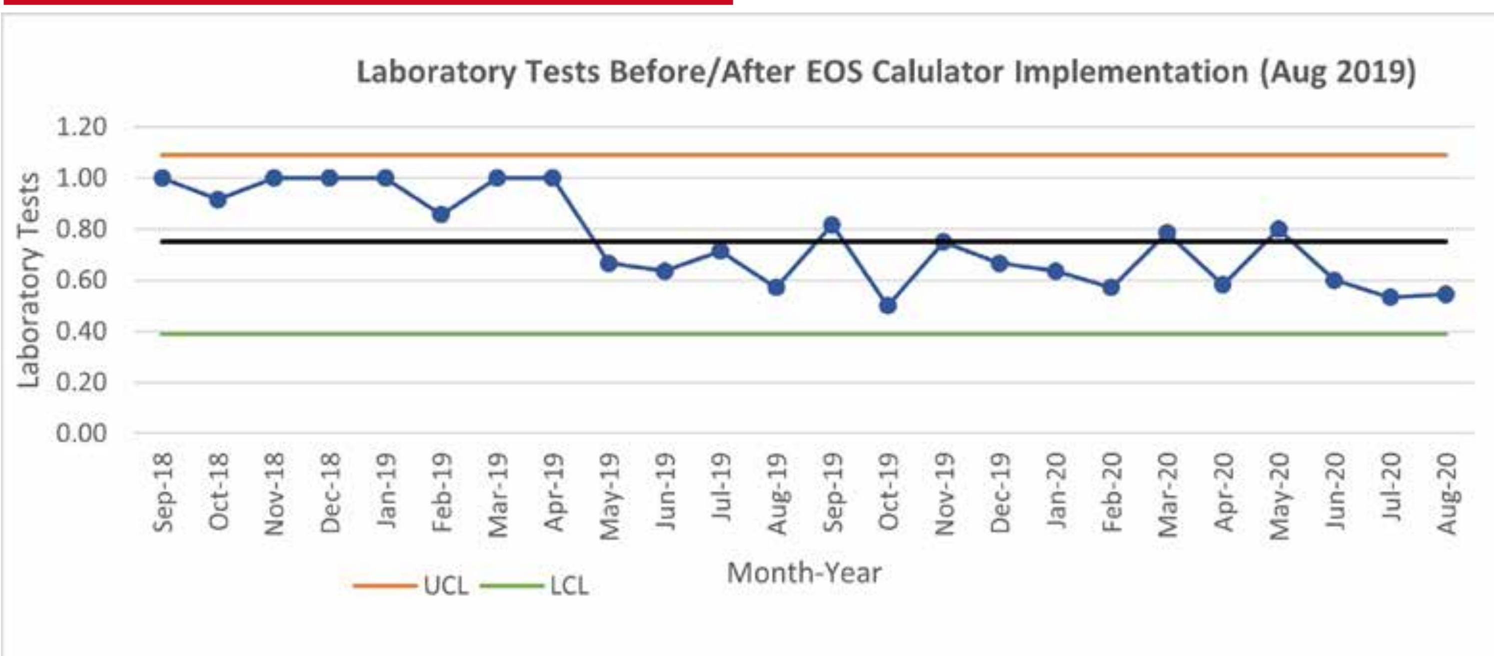
(a) n (Percentage); (b) Median (Interquartile range)

With all types of sepsis, the average reported LOS was 24 to 72 days in high-income countries. (18) The United States, in particular, has the highest treatment costs worldwide, spending almost twice as much on medical care as ten other high-income countries with comparatively worse healthcare outcomes. (2) This study sought to determine whether using the EOS calculator decreases sepsis evaluations, antibiotic utilization, and hospital LOS for newborns whose mothers were diagnosed with confirmed chorioamnionitis (CAM) and its cost implications at our facility.

"With all types of sepsis, the average reported LOS was 24 to 72 days in high-income countries. (18)"

Methods

A retrospective observational cohort study was conducted at a metropolitan area hospital with approximately 6 000 deliveries annually. Any mother with a pregnancy ≥ 35 weeks gestation diagnosed with CAM was screened for inclusion (N = 249). ICD-10-CM codes for chorioamnionitis (041.1230, 041.1290) were used to extract information from the hospital data warehouse. Direct admissions to the neonatal intensive care unit (NICU) were excluded as these infants likely would have been symptomatic for sepsis and would require antibiotic therapy, thus eliminating the need for the EOS calculator. De-identified information, including demographic and clinical characteristics, antibiotic usage (initiation, number of days), EOS-related laboratory tests (CBC and blood culture), and LOS, were collected one year before and after the August 28, 2019, EOS calculator implementation. In our unit, we currently



use the Center for Disease Control's national incidence of EOS (0.5/1000 live births) when computing the probability of sepsis. Our current antibiotic regimen for a newborn at risk for early infection is, at minimum, treatment with 48 hours of IV antibiotics. Ampicillin is prescribed at 100mg/kg every 8 hours for six doses and Gentamicin 4 mg/kg every 24 hours for two doses. Readmissions throughout the hospital system within 14 days of discharge were reviewed for any diagnosis of sepsis. The estimated hospital reimbursement associated with EOS-related laboratory tests and antibiotic treatment (IV antibiotic administration and physician fee) was calculated for each cohort using the Arizona Medicare reimbursement rates for 2018-2020.

Human protection oversight was obtained from the Banner Health Institutional Review Board, and the study can be found on Clinicaltrials.gov as NCT04513691. Due to the retrospective nature of this study, the data retrieval did not undergo independent monitoring.

Statistical Analysis

Descriptive statistics were used to summarize the data for all study variables. Continuous variables were reported as means and standard deviation values. Categorical variables were reported as numbers and percentages. All categorical variables were compared using the Fisher exact or $\chi 2$ test, and the Wilcoxon Rank Sum test was applied for continuous variables. In addition, monthly charts were plotted for labs and antibiotic usage. By using an estimated 40% and 23% antibiotic usage rate for pre/post-intervention, respectively, a sample size of at least 234 subjects was needed, assuming an alpha level of 0.05 and 80% power. STATA® Version 17 (StataCorp, College Station, TX) was used for all statistical analyses. A P value < 0.05 was considered significant.

"There were no significant differences in the demographics between the two cohorts; however, more than half of the mothers in both groups identified as Hispanic (Table 1). Both cohorts had a median gestational age of 39 weeks; the median birthweight in grams was 3400 vs. 3440."

Results

Of the 249 mother and baby dyads reviewed, 236 were included in this study. There were 111 newborns in the pre-EOS calculator cohort and 125 in the post-cohort. There were no significant differences in the demographics between the two cohorts; however, more than half of the mothers in both groups identified as Hispanic (Table 1). Both cohorts had a median gestational age of 39 weeks; the median birthweight in grams was 3400 vs. 3440. As expected, there was a significant decrease in EOS-related laboratory tests after implementing the calculator (97 vs. 87, $P < 0.001$). Additionally, antibiotic usage was significantly lower, with the number of courses decreasing by over 50% (89 vs. 40, $P < 0.001$). This resulted in a reduction of median antibiotic days in the post-implementation cohort (2 vs. 0, $P < 0.0001$) (Table 2). When graphed by month (Figures 1, 2), a decrease in the proportion of laboratory tests and antibiotic usage is apparent after calculator implementation antibiotics usage ($210.60 vs. $85.20; $P < 0.0001$) was significantly reduced. There was a statistically significant reduction in the median combined estimated reimbursement associated with EOS-related care per baby ($292.23 vs. $34.34; $P < 0.0001$) (Table 2). When reviewing for readmissions to the hospital network for missed EOS cases, none were present.

"As expected, there was a significant decrease in EOS-related laboratory tests after implementing the calculator (97 vs. 87, P < 0.001). Additionally, antibiotic usage was significantly lower, with the number of courses decreasing by over 50% (89 vs. 40, P < 0.001)."

Discussion

As mirrored elsewhere in the literature, using the EOS calculator has proven beneficial to our hospital. We observed a significant reduction in laboratory tests and antibiotic usage by adopting the EOS calculator, ultimately decreasing the cost burden. The large meta-analysis conducted by Atchten et al. (19) supports our findings, which reviewed over 175,000 neonates. They confirmed that using the EOS calculator results in a substantial reduction in empirical antibiotics. (19) The change in practice is especially beneficial to newborns whose mothers were diagnosed with CAM placing them at the highest risk of receiving EOS treatment. Eliminating prophylactic treatment when the risk of EOS is low allows the newborn and mother to remain together to establish breastfeeding and bond. It also decreases the economic burden on the hospital system when well-appearing infants do not need to receive antibiotic treatment. (1)

"We observed only a slight reduction in LOS, which was not statistically significant. Nevertheless, in a similar study to ours, Achten et al. (20) found that the mean LOS for EOS was significantly shorter for their post-implementation cohort (0.37 days, P = 0.005)."

Another advantage of utilizing the calculator is its effect on hospital LOS. We observed only a slight reduction in LOS, which was not statistically significant. Nevertheless, in a similar study to ours, Achten et al. (20) found that the mean LOS for EOS was significantly shorter for their post-implementation cohort (0.37 days, P

= 0.005).

We used the actual Arizona Medicare reimbursement rates to determine our facility's estimated compensation for EOS. Reducing the number of laboratory tests and antibiotic usage decreased the median cost burden by $257.89 ultimately. Gong et al. (21) performed a cost-benefit analysis in which usage of the EOS calculator showed a net monetary benefit of $3998 per infant, which may largely be attributed to the 67% reduction in antibiotic therapy.

Atchen et al. (19) further found that using the EOS calculator did not lead to an increase in missed cases of EOS, overall EOS incidence, readmissions, delay in antibiotic therapy, or EOS-related morbidity or mortality. Leonardi et al. (1) found similar results regarding the lack of hospital readmissions due to sepsis, similar to our study. Likewise, we showed the absence of readmissions for EOS and any sepsis 14 days after the newborn's initial discharge.

"As is true for any dataset, errors in coding or labeling may have inadvertently caused some patients to be omitted. Our sample size did not demonstrate a significant reduction in LOS, but a more extensive study may detect improvement."

Limitations

Although our results are in line with many other publications, this study was conducted at a single hospital in a higher-income country, and thus, Arizona Medicare reimbursement rates may not be generalizable to other sites worldwide. In contrast to individual chart reviews, we could access the hospital's databases and review the de-identified information quickly. However, we could not explore individual medical records to gather specific details of interest. As is true for any dataset, errors in coding or labeling may have inadvertently caused some patients to be omitted. Our sample size did not demonstrate a significant reduction in LOS, but a more extensive study may detect improvement.

Additionally, the delivery mode may have impacted the infant's total LOS. As we did not evaluate infants admitted to the NICU, our hospital's true incidence of EOS was not captured. Prenatal antibiotic administration was not collected; therefore, it is unknown what effect it may have had on a newborn's clinical course.

Conclusion

This study contributes to the currently available literature advocating using the EOS Calculator. The judicious clinical observation of the newborn and calculator use safely reduces sepsis evaluations, antibiotic administration, and resource utilization.

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