Use of a Modified Early-Onset Sepsis Risk Calculator for Neonates Exposed to Chorioamnionitis

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Objective To validate the recently modified Kaiser Permanente early-onset sepsis (EOS) calculator with a higher baseline incidence in chorioamnionitis exposed neonates.

Study design This is a retrospective study of chorioamnionitis-exposed neonates born at ≥35 weeks of gestation with a known EOS incidence of 4.3/1000. The risk and management categories were calculated using the calculator with an incidence of 4/1000. The results were compared with a previous analysis of the same cohort that used an EOS incidence of 0.5/1000.

Results In our sample, the EOS calculator recommends at least a blood culture in 834 of 896 (93.1%) and empiric antibiotics in 533 of 896 (59.5%) chorioamnionitis-exposed neonates when using an EOS incidence of 4/1000. This captures 5 of 5 neonates (100%) with EOS. When using a baseline EOS incidence of 0.5/1000, the calculator recommends at least a blood culture in only 289 of 896 (32.2%) and empiric antibiotics in only 209 of 896 (23.3%) neonates, but fails to recommend empiric antibiotics in 2 of 5 neonates with EOS (40%).

Conclusions When using an EOS risk of 4 of 1000 in infants exposed to mothers with chorioamnionitis, the EOS calculator has the ability to capture an increased number of neonates with culture-positive EOS. However, this change also leads to nearly a 3-fold increase in the use of empiric antibiotics and an evaluation with blood culture in almost all infants born to mothers with chorioamnionitis. *(J Pediatr 2019;213:52-7)*.

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Chorioamnionitis (intra-amniotic infection), is a common complication of pregnancy, occurring in 1%-10% of all term deliveries, and is a major risk factor for early-onset sepsis (EOS) in neonates[1,2] Previous recommendations from the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics' Committee on the Fetus and Newborn (COFN) were for a blood culture, complete blood count, and empiric antibiotics pending blood culture results for all neonates exposed to maternal chorioamnionitis, even if well appearing.[3,4] The risk of EOS in infants exposed to chorioamnionitis, however, is significantly decreased to as low as 0.14%-0.70% with the use of intrapartum antibiotics.[1,5] To pre-emptively treat the rare case of EOS, large numbers of uninfected infants will be exposed to multiple laboratory testings and systemic antibiotics, and in some institutions such infants are admitted to the neonatal intensive care unit (NICU) and separated from their mothers.

In an attempt to decrease the use of antibiotics and evaluation for sepsis in infants born to mothers suspected to have chorioamnionitis, several new strategies have undergone evaluation. The COFN recently published new recommendations for a framework of evidence-based approaches to sepsis risk assessment, in which infants can be stratified by the level of risk for EOS. Acceptable approaches to risk stratification may include categorical algorithms that use threshold values for intrapartum risk factors, serial physical examinations alone to detect the presence of clinical signs of illness after birth, and multivariate risk assessments based on both intrapartum risk factors and infant examinations.[6] The EOS calculator is an example of this last approach. Investigators at Kaiser Permanente developed the EOS calculator using a cohort of 350 cases of culture proven EOS among 608 000 neonates born at ≥34 weeks of gestation. This calculator provides clinicians with a tool to determine multivariate EOS risk among term and late preterm infants by combining both antepartum and intrapartum factors with the neonate's clinical status to provide a final estimated risk of EOS and recommendation for management.[7] The calculator has not been validated prospectively for use in a population of neonates with a higher baseline risk of sepsis.

CDC	Centers for Disease Control and Prevention
COFN	Committee on the Fetus and Newborn
EOS	Early-onset sepsis
NICU	Neonatal intensive care unit

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We have reported that ~25% of clinicians in the US use the EOS calculator for the management of neonates exposed to chorioamnionitis.[8] However, the original calculator was designed to estimate the risk of EOS in all neonates born at ≥34 weeks of gestation and used a baseline incidence for EOSwhich reflected that population. The risk of EOS is many folds greater in the subset of neonates exposed to chorioamnionitis. Experts have raised concerns about the use of the EOS calculator in neonates born to mothers with chorioamnionitis and have suggested using a baseline risk of EOS in this subpopulation.[9] We have previously reported that the use of EOS calculator in these neonates is likely to miss infants with blood culture-positive EOS.[10]

Recently, the EOS calculator was modified to estimate the risk of sepsis using a higher baseline incidence of up to 4/1000 live births, which more closely estimates the risk of EOS in our institution among infants exposed to chorioamnionitis (4.3/1000 live births). The objective of our study was to evaluate the performance of the modified EOS calculator in neonates born to mothers with chorioamnionitis using this revised baseline incidence.

Methods

The cohort included neonates with gestational ages of ≥35 weeks born to mothers with clinical chorioamnionitis between November 2006 and March 2017 and admitted to a level III NICU. The Institutional Review Committee at Thomas Jefferson University Hospital approved this study. Neonates exposed to chorioamnionitis were identified from a neonatal database (Neodata; Isoprime, Lisle, Illinois). Relevant demographic, clinical, and laboratory data were collected. The diagnosis of chorioamnionitis was made by an obstetrician based on intrapartum fever (temperature of ≥38°C) alone or in conjunction with maternal leukocytosis, uterine tenderness, foul-smelling amniotic fluid, and maternal or fetal tachycardia. All neonates born to mothers with chorioamnionitis at our institution were admitted to the NICU. A blood culture was obtained and empiric antibiotic therapy was initiated.

We reviewed the neonates' charts and collected data for entry into the EOS calculator to determine a baseline risk of EOS at birth. These data included the highest maternal antepartum temperature, gestational age, duration of maternal membrane rupture, maternal colonization with group B streptococcus, and the type and timing of intrapartum antibiotic therapy. We then classified each neonate as well appearing, equivocal, or with clinical illness using the signs and symptoms described on the Kaiser Permanente website (https://neonatalsepsiscalculator.kaiserpermanente.org). Each neonate's EOS risk was determined using the EOS calculator, with the incidence of the EOS variable set at 4/1000 live births based on the EOS incidence of 4.3/1000 live births in the population of infants exposed to chorioamnionitis in our NICU.[10]

After data entry into the EOS calculator, management recommendations were obtained and recorded. Management recommendations fall into 5 categories: blood culture and empiric antibiotics, blood culture and vital signs every 4 hours, strongly consider antibiotics, vital signs every 4 hours, and observation only. These recommendations were compared with those from our previous analysis of the same cohort of neonates using an EOS incidence of 0.5/1000 (CDC national incidence).[10] Statistical evaluation was performed using the Sigma Stat 3.1 for Windows statistical package (Systat Software, Point Richmond, California). Comparisons between the groups were performed using the Student *t* test and Mann-Whitney rank-sum test for continuous data, and the χ^2 or Fisher exact test for categorical data. Statistical significance was set at $P < .05$.

Results

There were 17 908 neonates born at ≥35 weeks of gestation during our study period, 1159 of whom were born to mothers with a diagnosis of clinical chorioamnionitis. Five of these neonates (0.43%) had culture-proven sepsis. Sufficient data to calculate the EOS risk were available for 896 neonates (77.3%), including all 5 neonates with positive blood cultures. Seventy-eight neonates were born to mothers who had a maximum temperature of <100.4°F but were included in our analysis owing to the mothers' obstetric diagnosis of clinical chorioamnionitis. A total of 896 neonates were included in the analysis. The patients' demographic and clinical characteristics are shown in Table I.

Table II depicts the EOS calculator management recommendations with baseline risk incidences set at both 0.5/1000 and 4/1000 live births. The median (IQR) risk of EOS at birth was significantly higher in the 4/1000 group compared with the 0.5/1000 group (6.72 [IQR, 3.91-12.04] vs 0.82 [IQR, 0.47-1.47]; $P < .0001$). Similarly, the median

Table I. Demographics and clinical characteristics of the study subjects (n = 896)

Characteristics	
Gestational age, weeks	39.4 ± 1.3
Birth weight, kg	3.35 ± 0.43
Male sex	477 (48.4)
African American Race	374 (41.7)
Group B streptococcus colonization	219 (24.4)
Duration of rupture of membranes, hours	13 (8-21)
Highest maternal temperature, °F	101 (100.6-101.6)
Apgar score at 5 minutes	9 (9-9)
No clinical illness	653 (72.9)
Clinical illness	142 (15.8)
Equivocal clinical illness	101 (11.3)
Positive blood cultures	5 (0.56)

Values are mean ± SD, median (IQR), or number (%).

Table II. Comparison of anticipated management recommendations using the calculator set at two baseline incidences of EOS (n = 896)

Characteristics	Baseline EOS incidence (0.5/1000)	Baseline EOS incidence (4/1000)	*P* value
Risk of EOS at birth (per 1000)	0.82 (0.47-1.47)	6.72 (3.91-12.04)	<.0001
Risk of EOS after clinical examination (per 1000)	0.5 (0.24-2.33)	4.11 (1.96-20.1)	<.0001
Blood culture and empiric antibiotics	209 (23.3)	533 (59.5)	<.0001
Blood culture and vital signs every 4 h	80 (8.9)	301 (33.6)	<.0001
Blood culture with or without empiric antibiotics	289 (32.2)	834 (93.1)	<.0001
Strongly consider antibiotics	2 (0.22)	0 (0)	.5
No blood culture, no antibiotics, vital signs every 4 h	207 (23.1)	52 (5.8)	<.0001
No blood culture, no antibiotics, no vital signs every 4 h	398 (44.4)	10 (1.1)	<.0001
Recommend blood culture with or without empiric antibiotics in infants with culture positive EOS	3/5 (60)	5/5 (100)	.44

Values are median (IQR) or number (%).

risk of EOS following clinical evaluation was greater in the 4/1000 group compared with the 0.5/1000 group (4.11 [IQR, 1.96-20.1] vs 0.5 [IQR, 0.24-2.33]; $P < .0001$). Blood culture and empiric antibiotics were recommended for 59.5% of infants when EOS risk was calculated using the baseline incidence of 4/1000. The recommendation for blood culture plus empiric antibiotics was significantly lower (23.3%; $P < .0001$) when the EOS risk was calculated using the lower baseline incidence of 0.5/1000 live births. At least a blood culture with or without empiric antibiotic therapy was recommended in 834 neonates (93.1%) in the 4/1000 group compared with 289 neonates (32.2%) in the 0.5/1000 group ($P < .0001$). Routine care (no empiric antibiotics, no blood culture, and no vital signs every 4 hours) was recommended for only 10 infants (1.5%) when the baseline incidence of 4/1000 live births was used.

When using a 4/1000 baseline risk, the EOS calculator recommended a blood culture and empiric antibiotics for all 5 neonates in our sample with blood culture-positive sepsis (Table III). Blood culture and empiric antibiotics were only recommended for 3 of 5 neonates (60%) when a 0.5/1000 baseline risk was used. Using the definitions of clinical symptoms from the EOS calculator, only 142 out of 896 neonates (15.8%) presented with clinical illness (Table IV). The calculator recommended a blood culture and empiric antibiotics for all of these infants. Six hundred fifty-three of 896 neonates (72.9%) were well appearing, and the EOS calculator recommended blood culture plus empiric antibiotics in 290 (44.4%) of these infants, and at least a blood culture (with or without empiric antibiotics) in 591 neonates (90.5%).

Discussion

Despite limited data, the Kaiser Permanente EOS risk calculator is increasingly being used in neonates born to mothers with suspected diagnosis of chorioamnionitis.[7] We and others have reported that the use of the EOS calculator in neonates exposed to chorioamnionitis is likely to miss cases of EOS.[10,11] Recently, the calculator was modified to allow input of a higher baseline risk of EOS, such as is found in neonates exposed to chorioamnionitis. In our cohort of infants born to mothers with chrioamnionitis, using the calculator with a higher baseline risk captured all culture-positive cases of EOS. However, setting a higher baseline risk also increased the frequency of evaluation with blood culture by 4-fold and the recommendation for empiric antibiotics by approximately 3-fold and as compared with the current most common practice of using a lower baseline risk of EOS.

Currently, there is wide practice variation in the approach of evaluating risk of EOS and treating newborns exposed to chorioamnionitis. Strictly following the 2012 CDC and the COFN guidelines for management of neonates born to mothers with clinical chorioamnionitis leads to the overtreatment of many uninfected infants. However, several studies have shown that the current risk of EOS in neonates exposed to chorioamnionitis is very low, and that antibiotic use may alter the gut microbiome, increasing the risk of late-onset

Table III. Comparison of management recommendations for infants with culture-positive EOS using 2 baseline EOS incidences

		Baseline EOS incidence (0.5/1000)			Baseline EOS incidence (4/1000)		
Neonates with culture-positive EOS	Clinical examination	Risk at birth	Risk with symptoms	Recommendation	Risk at birth	Risk with symptoms	Recommendation
Group B *streptococcus*	Well-appearing	4.02	1.65	Blood culture and vital signs every 4 h	32.26	13.48	Blood culture and empiric antibiotics
Escherichia coli	Well-appearing	2.39	0.98	Observation and vital signs every 4 h	19.4	8.05	Blood culture and empiric antibiotics
α-Hemolytic *streptococcus*	Equivocal	5.15	25.25	Blood culture and empiric antibiotics	41.03	176.23	Blood culture and empiric antibiotics
Streptococcus intermedius	Clinical illness	3.44	68.19	Blood culture and empiric antibiotics	27.66	376.33	Blood culture and empiric antibiotics
Streptococcus sanguinis	Clinical illness	2.03	41.34	Blood culture and empiric antibiotics	15.56	263.1	Blood culture and empiric antibiotics

Table IV. Management recommendations by EOS calculator in infants based on clinical examination using baseline risk of 4/1000 live births (n = 896)

Calculator recommendations	Well appearing (n = 653)	Equivocal (n = 101)	Clinical illness (n = 142)
Blood culture plus empiric antibiotics	290 (44.4)	101 (100)	142 (100.0)
Blood culture plus vital signs every 4 h	301 (46.1)	3 (3.0)	0 (0)
Blood culture with or without empiric antibiotics	591 (90.5)	0 (0)	0 (0)
Strongly consider antibiotics	0 (0)	0 (0)	0 (0)
No blood culture, no antibiotics; vital signs every 4 h	52 (8.0)	0 (0)	0 (0)
No blood culture, no antibiotics, no vital signs every 4 h	10 (1.5)	0 (0)	0 (0)

Values are number (%).

infection and affecting early immune programming, as well as increasing risk of asthma, obesity, and autoimmune disorders in later childhood and adulthood.[1,10,12-17] Neonates born to mothers with chorioamnionitis also frequently are admitted to the NICU, which can interfere with bonding and breast feeding, prolong the length of hospitalization, and increase the risk of medical errors and treatment complications.[1,18,19] Evaluating and treating with antibiotics every neonate born to mothers with chorioamnionitis therefore places a large burden on healthcare costs. Improved means of identifying the chorioamnionitis exposed neonates at highest risk of EOS are needed to minimize antibiotic exposure and evaluation for sepsis for those with minimal risk.

The objective of the first Kaiser Permanente EOS risk calculator, developed in 2012, was to establish a prior probability of newborn sepsis that could then be combined with postnatal physical examination to establish a posterior probability of EOS and potentially decrease the number of low-risk infants evaluated for infection.[7,20] The calculator has been modified several times since its development. In 2014, a risk stratification strategy was added to the calculator that combined objective perinatal data with evolving objective neonatal clinical signs and symptoms to achieve more a more specific means for the evaluation and treatment of EOS. Newborns were placed into 1 of 3 clinical categories: clinical illness, equivocal presentation, and well appearing. The risk of EOS generated by the EOS risk calculator plus the clinical category of the newborn could then be combined to lead management into 1 of 3 categories: treat empirically, observe and evaluate, or continued observation alone.[20] Two additional management categories have since been added: vital signs every 4 hours and strongly consider antibiotics.

The authors of the EOS calculator analyzed a cohort of all neonates born at ≥35 weeks of gestation during the study period.[21] The cohort consisted of 204 485 infants, which included 51 infants (0.25/1000) with culture-proven EOS. After the implementation of the EOS calculator at the study institution, blood culture testing decreased from 14.5% to 4.9% and antibiotic use decreased from 5.2% to 2.6%. However, the calculator performed poorly in predicting EOS and recommending empiric antibiotics in this cohort. In 51 infants with blood culture-positive EOS, the calculator would have failed to recommend empiric antibiotics in 31 (60.8%) or a blood culture in 25 (49%). During the period of EOS calculator use only, the calculator failed to identify and recommend empiric antibiotics in 50% (6 of 12) of initially low-risk infants who later had a positive blood culture. Five of these infants developed symptoms later during the birth hospitalization and the sixth infant with a positive blood culture was never symptomatic. This finding suggests the potential for a significant delay in evaluation, particularly from the time of blood culture draw to the time of antibiotic therapy. Despite the poor performance of the EOS calculator in recommending the timely evaluation of infants with EOS, and concerns expressed by experts regarding length of stay and incidence of systemic complications owing to delayed sepsis evaluation and antibiotic administration, the use of the EOS calculator is increasing, including in the subset of neonates exposed to chorioamnionitis.[7,22] More recently, others also have reported instances of blood culture-positive EOS cases that would have been missed by use of the EOS calculator.[9,10,23]

The initial EOS calculator gave the option of choosing a baseline risk of sepsis of 0.3/1000 to 0.6/1000 live births based on the EOS incidence rate that is most consistent with the user's institution. The prevalence of sepsis, defined by a positive culture from blood or cerebrospinal fluid, in the original study population by the Kaiser Permanente network was 0.58/1000 live births.[7,20] This was similar to the CDC reported national incidence of EOS of 0.5/1000 live births.[3] Recently, however, a concern was raised that the EOS calculator should not be used in a subpopulation of neonates with a different baseline prevalence of sepsis.[9] The incidences of EOS reported in neonates born to mothers with clinical chorioamnionitis have been 4.3/1000 live births to 7/1000 live births, 11% for neonates born to mothers who had a histologic diagnosis of chorioamnionitis, and 15% in neonates admitted to the NICU.[10,24-26] In recognition of these findings, in July 2018 the EOS calculator was expanded to include a range of prior probabilities for sepsis risk from 0.1/1000 to 4/1000, a range that still does not permit selection of higher baseline incidence relevant in some institutions. The use of higher prevalence rates of sepsis results in increasing recommendations for management with blood culture and empiric antibiotics.

With the use of a low baseline EOS risk in our cohort, the calculator would have decreased the evaluation for sepsis and antibiotic use by nearly 68%; however, among 5 infants with blood culture-positive EOS, the calculator would have recommended no empiric antibiotics in 2 patients and no blood

culture in 1 patient.[10] No infant with blood culture-positive EOS was missed by applying the sepsis calculator with a modified higher baseline incidence of 4/1000 live births, which closely approximated the incidence of EOS in our cohort. However, performance of a blood culture would be nearly 4-fold higher and use of antibiotics would be nearly 3-fold higher.

If the EOS calculator with a baseline risk of 4/1000 live births had been applied in our cohort, 59.5% of neonates would have received empiric antibiotics, whereas 100% of our neonates received antibiotic treatment owing to our institution's extant adherence to the CDC and COFN guidelines. With the approximate 7%-10% of neonates born to mothers with a diagnosis of chorioamnionitis, the use of empiric antibiotics in 59.5% of their neonates still results in large numbers of neonates being administered empiric antibiotics.[23,27] Moreover, by setting a higher baseline risk of sepsis, 93% of the neonates in our cohort would have required evaluation with at least a blood culture plus close monitoring of vital signs. In institutions with higher baseline risks of EOS (7-150/1000 live births), an adjusted calculator likely would recommend empiric antibiotics in almost every neonate born to mothers with clinical chorioamnionitis.

The EOS calculator is designed to estimate the risk of EOS in all neonates born at ≥34 weeks of gestation. Several small retrospective studies have attempted to validate the use of the EOS calculator in the neonatal population exposed to chorioamnionitis, but have used the calculator setting at low risk, have small numbers, and are lacking cases of confirmed EOS. All showed substantial decreases in testing and antibiotic use, but safety was not evaluable.[5,11,28,29] The most recent version of Kaiser Permanente EOS calculator probably is not suitable for use in the subpopulation of neonates born to mothers with chorioamnionitis. There may actually be a potential for overestimating the risk of EOS when both maternal fever and a higher baseline sepsis risk are used, because maternal fever already serves as an objective measure of intra-amniotic infection or inflammation in the calculator algorithm. The expert panel at the National Institute of Child Health and Human Development suggested using a more rigorous definition of intra-amniotic infection (intra-amniotic inflammation or infection or both, abbreviated as triple I).[30] A more rigorous definition potentially can decrease empiric antibiotic use and evaluation for sepsis in infants. A combination of approaches proposed by the COFN and the expert panel at the National Institute of Child Health and Human Development may be safer and is worthy of study. Factors should include the EOS calculator multivariate risk assessment, categorical risk factor assessment based on intrapartum factors, and a risk assessment based on the infant's clinical condition.[6]

The strength of our study is the large sample size of exposed neonates managed strictly by the 2012 CDC and COFN guidelines for infants born to mothers with a diagnosis of clinical chorioamnionitis, and a greater proportion of infants has culture-positive EOS compared with other studies.[5,28,29] Furthermore, we used the modified EOS calculator with the highest available setting for baseline sepsis incidence. Our study has limitations. It was performed retrospectively at a single center. We excluded a number of neonates owing to insufficient information needed to calculate EOS risk, none of whom had culture-positive EOS. Only 5 infants in our cohort had culture-proven sepsis, precluding the validation of the safety of the EOS calculator. A larger prospective study is required to establish the safety and proficiency of the Kaiser Permanente EOS risk calculator in the subgroup of infants born to mothers with chorioamnionitis. ■

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