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Infants Born to Mothers with Clinical Chorioamnionitis: A Cross-Sectional Survey on the Use of Early-Onset Sepsis Risk Calculator and Prolonged Use of Antibiotics

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Abstract

Objective—To evaluate variations in practice for the management of neonates born to mothers with clinical chorioamnionitis.

Methods—This was a prospective cross-sectional survey consisting of 10 multiple choice questionnaires distributed to 2,900 members of the Perinatal Section of American Academy of Pediatrics. Variations in responses were assessed and compared between the various groups.

Results—A total of 682 members (23.5%) completed the survey; 169 (24.8%) indicated that they use the neonatal early-onset sepsis (EOS) risk calculator for the management of neonates born to mothers with clinical chorioamnionitis. More respondents from the western region of United States and level III units are using the EOS risk calculator compared with the south and level II units. Approximately 44% of the respondents indicated that they will not stop antibiotics at 48 to 72 hours in asymptomatic neonates born to mothers with chorioamnionitis with negative blood culture if the complete blood count (CBC) and C-reactive protein (CRP) are abnormal.

Conclusion—A large number of practitioners are using the neonatal EOS risk calculator for neonates born to mothers with chorioamnionitis. Despite a clear guideline from the Committee on Fetus and Newborn, almost 44% will treat healthy-appearing neonates born to mothers with chorioamnionitis with a prolonged course of antibiotics solely for abnormal CBC or CRP.

Keywords

sepsis; neonates; EOS calculator; maternal fever

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Conflict of Interest

None.

Clinical chorioamnionitis is a significant risk factor for early-onset sepsis (EOS) in neonates, and it remains a complication in 1 to 10% of pregnancies in the United States.[1–4] The risk of EOS is dramatically reduced with the use of intrapartum antibiotics.[5–7] Recent studies have shown that the risk of EOS in neonates born to mothers with clinical chorioamnionitis is as low as 0.14 to 0.7%.[3,8] The Centers for Disease Control and Prevention (CDC) and the Committee on Fetus and Newborn (COFN) recommend that newborns whose mothers are diagnosed with clinical chorioamnionitis have a blood culture and complete blood count (CBC) drawn, along with initiation of empiric antibiotic treatment pending blood culture results.[1,2] As a result of this recommendation, a large number of uninfected neonates are exposed to systemic antibiotics, separated from their mothers and admitted to the neonatal intensive care unit (NICU).

In an effort to improve the assessment of the riskof EOS and limit antibiotic use in neonates, several new strategies are under evaluation. The investigators at the Kaiser Permanente have developed the EOS calculator using a cohort of 350 cases of culture-proven EOS among 608,000 neonates born at 34 weeks of gestation.[4] The calculator uses the highest maternal antepartum temperature, gestational age, the length of time a mother's membranes were ruptured, group B streptococcus carriage status, and type and timing of intrapartum antibiotic therapy to assign a preliminary risk score of EOS. It then combines this result with the neonate's clinical status to give a final risk of EOS and a recommendation for management. The EOS calculator has been modified several times and the most recent version is available at: https://neonatalsepsiscalculator.kaiserpermanente.org. Despite limited data on the use of EOS calculator in the subpopulation of neonates born to mothers with chorioamnionitis, the EOS risk calculator is increasingly being used by the clinicians to limit antibiotic use.

The COFN also recommends CBC and optional C-reactive protein (CRP) testing at 6 to 12 hours of age in neonates born to mothers with clinical chorioamnionitis.[2] However, there is no clear guidance on how to use these laboratory tests in the management of neonates exposed to chorioamnionitis. The COFN recommends discontinuation of antibiotics at 48 to 72 hours of age if the blood culture is negative and the neonate remains asymptomatic, even if the laboratory tests are abnormal. However, due to intrapartum use of antibiotics and technical pitfalls, neonatologists are concerned that blood cultures may not be reliable for the diagnosis of EOS in neonates born to mothers with chorioamnionitis who are pretreated with antibiotics. The clinicians are uncomfortable in stopping antibiotics if CBC or CRP is abnormal even if the blood cultureis negative and neonates are asymptomatic and often treat such infants with a longer course of antibiotics (5–7 days).

The objective of our survey was to evaluate variations in practice for the management of neonates born to mothers with clinical chorioamnionitis. We were specifically interested in evaluating the use of EOS risk calculator for the management of neonates born to mothers with chorioamnionitis. We also surveyed clinicians on the management of healthy-appearing, chorioamnionitis-exposed neonates who have abnormal CBC and CRP and negative blood cultures.

Methods

A prospective cross-sectional quantitative survey consisting of a case presentation followed by 10 multiple-choice questions was designed using an online survey tool as shown in Table 1. Respondents were allowed to choose one answer. Demographic questions included region of practice, years of experience, level of the NICU, and affiliation with a teaching institution. The rest of the survey included multiple-choice questions to identify variations in practice when treating asymptomatic neonates born to the mothers with clinical chorioamnionitis who have abnormal CBC or CRP and negative blood culture.

The survey was distributed electronically on August 2016 with a reminder on October 2016. Clinicians were identified from the Perinatal Section of American Academy of Pediatrics (AAP). The questionnaire was distributed to 2,900 members (2,450 neonatologists, 300 neonatology fellows, and 150 neonatal nurse practitioners). Participation in the survey was voluntary and the respondents' identity was unknown to the investigators. The protocol was exempted from a full review by the Institutional Review Board at Thomas Jefferson University.

We presented to responders a well-appearing term neonate born to mother with clinical chorioamnionitis. The infant remained asymptomatic throughout the NICU stay and had a negative blood culture but abnormal CBC and CRP. We asked the participants of the survey whether they use the EOS risk calculator for managing a neonate born to mothers with clinical chorioamnionitis. The following questions assessed the providers' preference for further testing of CBC and CRP at a later time, as well as the decision to perform a lumbar puncture. It was specifically emphasized that the blood culture remained negative and the infant is well appearing. Finally, we assessed the responders' preference for the duration of treatment with antibiotics, giving options ranging from 48 hours to 7 days. The responses were compared between clinicians with <or> 5 years of experience, practicing in teaching versus nonteaching institutions, levels of the NICU, and region of the country. Statistical analysis was performed using the Sigma Stat 3.1 for Windows statistical package (Systat Software, Inc., Point Richmond, CA) using the chi-square or Fisher's exact test and level of significance was set at $p < 0.05$.

Results

The survey was distributed to 2,900 participants, and 682 clinicians completed the survey with a response rate of 23.5%. Approximately, 25% (169/682) of all respondents use the EOS risk calculator for the management of neonates born to mothers with clinical chorioamnionitis (►Table 2). Thirty-one per cent of responders from the west use EOS risk calculator compared with 20% from the south ($p = 0.03$). The clinicians from a level III NICU are more likely (31%) to use the EOS calculator than from a level II NICU (14%). There was no significant difference in EOS calculator use in clinicians from the teaching versus nonteaching institutions or > 5 years of experience versus < 5 years of experience (►Table 2).

When asked about the management of a healthy-appearing neonate born to mothers with clinical chorioamnionitis with an abnormal CBC and CRP at 6 to 12 hours, the majority (82%) of practitioners indicated that they would repeat the CBC and CRP testing at 24 hours. Another 39% would repeat CBC and CRP testing at 48 hours, if the second set of laboratories at 24 hours were abnormal.

When asked about the need for lumbar puncture in a healthy-appearing neonate born to a mother with chorioamnionitis, 4.8% of participants indicated that they would perform a spinal tap if the initial CBC and CRP were abnormal. Twenty-one per cent of responders would perform a lumbar puncture if the second CBC and CRP results at 24 hours were abnormal, even if infants remain well appearing on clinical exam and blood culture is negative.

Table 3 provides the distribution of responses for the management of asymptomatic neonates born to mothers with chorioamnionitis with abnormal CBC and CRP at 12 and 24 hours of life, negative blood culture, and normal cerebrospinal fluid (CSF) if a lumbar puncture was performed. Only 56% of respondents would stop antibiotics at 48 to 72 hours (49% at 48 hours and 6% at 72 hours). More than 27% of practitioners elected to treat well-appearing neonates with a negative blood culture for 5 to 7 days of broad-spectrum antibiotics based solely on abnormal CBC and CRP results. Another 16.4% respondents would wait for the 48-hour CBC and CRP results to decide the duration of antibiotic therapy. The responses to continue antibiotic beyond 48 to 72 hours were uniform in all regions, all levels of the NICU, teaching or nonteaching hospitals, and the experience of the clinicians (►Table 4).

Discussion

As the CDC and the COFN recommend blood culture and initiation of empiric antibiotics in every neonate born to mothers with clinical chorioamnionitis, a large number of infants are admitted to the NICU and treated with systemic antibiotics. To limit the use of antibiotics in neonates, the investigators from the Kaiser Permanente developed the EOS risk calculator based on a large retrospective database.[4] Despite limited data on the use EOS risk calculator in neonates born to mothers with clinical chorioamnionitis, our survey indicates that approximately 25% of practitioners use the calculator. The COFN also recommends CBC and an optional CRP at 6 to 12 hours of age for these neonates.[2] However, there is no clear guidance on how to use these laboratory tests in the management of neonates exposed to chorioamnionitis. The COFN recommends discontinuation of antibiotics at 48 to 72 hours of age if a blood culture is negative and the neonate remains asymptomatic even if the laboratory tests are abnormal.[9] However, our survey indicates that a large number of clinicians would use a prolonged course of antibiotics in well-appearing term infants born to mothers with clinical chorioamnionitis solely on the basis of abnormal CBC and CRP results, even if the blood culture was negative.

Strictly following the CDC and the COFN guidelines for management of neonates born to mothers with clinical chorioamnionitis leads to overtreatment of many uninfected infants. This management strategy was designed for maximum reduction of EOS with acceptance of significant overtreatment. However, we and others have shown that the risk

of EOS in neonates born to mothers with clinical chorioamnionitis is very low.[3,8,10,11] Moreover, recent studies have highlighted the potential adverse effects of neonatal antibiotic use including the risk for asthma, obesity, and autoimmune disorders later in life.[12–14] In hospitals where intravenous antibiotic therapy cannot be administered in newborn nursery, the existing guidelines for the management of neonates born to mothers with chorioamnionitis leads to unnecessary NICU admissions, separation of neonates from their mothers, and creates a huge burden of health care costs. Several new strategies are under evaluation to reduce the use of empiric antibiotics and sepsis evaluations in neonates born to mothers with chorioamnionitis. The EOS calculator has been shown to reduce both the number of sepsis evaluations and the use of systemic antibiotics in neonates at risk of EOS.[4,15] However, experts have raised the concern for missing or delaying antibiotic use by using the EOS risk calculator.[16] Kerste et al would have missed both of their neonates with positive blood culture if the EOS risk calculator was used in their cohort of 2,094 neonates born 34 weeks of gestation.[17] In a report from the authors of the EOS calculator, the use of antibiotics was reduced by approximately 50% with the use of the calculator in neonates born at > 34 weeks of gestation.[15] However, during the period of EOS calculator use, the calculator algorithm failed to identify and recommend empiric antibiotics in 50% (6 out of 12) of infants at birth who later had culture-proven EOS.[15] Moreover, during the baseline period when the EOS risk calculator was not in use, the estimated risk of EOS was very low (< 1 per thousand infants) in the majority of their infants (16 out of 24) with culture-proven EOS and at least in 10 infants (42%) with EOS, timely sepsis workup and empiric antibiotics would not have been initiated.[15] We also recently reported that the use of EOS risk calculator failed to recommend empiric antibiotics in two out of five infants with culture positive EOS in our cohort of 896 infants born to mothers with clinical chorioamnionitis.[10] In a recent report by Money et al, the only infant with culture positive EOS would have been missed by the EOS risk calculator if applied to a cohort of 362 well-appearing neonates born to mother with chorioamnionitis.[11] In addition to concerns about the performance of the EOS risk calculator, the implementation of the EOS calculator may not be feasible in every center as it requires manpower, training, and resources. The EOS calculator is designed to estimate the risk of sepsis in all neonates born at > 34 weeks of gestation and is not specific for infants born to mothers with chorioamnionitis.[4,15] Calculating the risk of EOS for all infants born at > 34 weeks of gestation not only increases provider workload but also has the potential for medical errors resulting from the miscalculation of EOS risk. Despite these limitations, it is concerning that 25% of participants in our survey are using the EOS risk calculator for the management of neonates born to mothers with clinical chorioamnionitis. It is interesting to note that there was no difference in the use of the EOS risk calculator in teaching and nonteaching institutions. The use of the EOS risk calculator for the management of infant born to mothers with clinical chorioamnionitis is increasing. In a previous survey conducted between October 2015 and January 2016, Mukhopadhyay et al reported that 11 out of 81 (13.6%) nurseries across 33 states in the United States were using the EOS risk calculator for managing neonates born to mothers with choriaomanionitis.[18] Based on our survey, the number of respondents using the calculator has almost doubled to 25% although regional variations and preferential response may contribute to this difference.

The COFN recommends performing a CBC and an optional CRP test at 6 to 12 hours of age in every neonate born to mothers with clinical chorioamnionitis.[2] However, there is no clear guidance from the COFN on how to use these laboratory tests for the management of neonates exposed to chorioamnionitis. Standard laboratory findings used to suspect sepsis in neonates such as leukocytosis, leukopenia, absolute band counts, absolute neutrophil counts, immature to total neutrophil ratio, and elevated CRP levels have limited positive predictive values (PPVs).[19–23] The CBC and CRP results have very poor PPV and positive likelihood (LRþ) ratio for the diagnosis of EOS in neonates. We have reported a PPV and LRþ of 4.4 and 8.25%, respectively, in neonates born to mothers with clinical chorioamanionitis.[10] The CBC and CRP results have an excellent negative predictive value and can be utilized for limiting sepsis evaluations and empiric antibiotics in neonates with low risk of EOS.[10] However, the CBC and CRP have limited utility in neonates whose sepsis workup is initiated and empiric antibiotics already started. The risk of EOS is reduced with the administration of antibiotics during labor and delivery to mothers with chorioamnionitis.[5,6] However, clinicians are concerned that the use of intrapartum antibiotics reduces the sensitivity of blood culture in neonates. The management of neonates exposed to chorioamnionitis and intrapartum antibiotics can be challenging for clinicians. As the blood culture may not be reliable due to maternal use of antibiotics and technical pitfalls, clinicians use abnormal laboratory test results as a surrogate marker for sepsis in neonates exposed to chorioamnionitis. In their earlier chorioamnionitis guidelines, the COFN recommended extending the duration of antibiotics in asymptomatic chorioamnionitis-exposed neonates, solely on the basis of abnormal screening laboratory tests.[2] Our publication in 2014 showed that by using the COFN guidelines, a large number of asymptomatic neonates were treated with prolonged antibiotics solely based on abnormal laboratory tests.[3] Based on our seminal publication, the COFN changed the guidelines stating that well-appearing infants with negative blood culture do not require antibiotics for more than 48 to 72 hours for isolated abnormal laboratory test results. However, our survey indicates that a large number of the providers still treat asymptomatic neonates with negative blood cultures, but with abnormal CBC and CRP results, with prolonged antibiotics with. Surprisingly, we found similar trends between teaching and nonteaching institutions. A recent expert opinion by Cantey and Baird clearly points out that the blood culture-negative sepsis remains a “medical myth” with no or limited evidence in conducted studies.[24] They argued that when the blood culture is drawn properly, its sensitivity approaches 100% when 1 mL of blood is inoculated and the infant has a bacterial concentration of as low as 1 to 4 colony-forming units per milliliter.[24] They further state that if the blood culture is negative after maternal intrapartum antibiotics prophylaxis, bacterial concentrations in the neonates are either reduced to ultralow concentrations or sterilized, neither of which requires additional antibiotic therapy.[24]

The COFN statements mentioned that the lumbar puncture is not needed in all infants with suspected EOS, especially if they appear healthy.[2] Lumbar puncture is recommended for infants with signs of sepsis, infants with positive blood culture, and for infants likely to be bacteremic on the basis of laboratory data. However, the COFN does not clearly define the abnormalities on laboratory data for performing lumbar puncture. Our survey indicates that the majority of providers will not perform lumbar puncture for an abnormal CBC and

CRP result. In a healthy-appearing neonate born to mother with chorioamnionitis, only 5% of participants indicated that they would perform a spinal tap if initial CBC and CRP are abnormal and another 21% of responders would perform lumbar puncture if second CBC and CRP at 24 hours are abnormal. Clearer guidelines are needed on performing lumbar puncture in healthy-appearing infants born to mothers with chorioamnionitis with abnormal laboratory data. Lumbar puncture is an invasive procedure and antibiotics are prolonged for another 48 to 72 hours while waiting for the CSF culture reports.

Our study has several important limitations. The survey was voluntary and only members of the Perinatal Section of the AAP participated in the study. The response rate for our survey was low. The members of the Perinatal Section of the AAP include also fellows, international scholars, and senior members. The members receive multiple surveys electronically via e-mail every month. The low response rate is likely to be due to survey fatigue from multiple studies and possible lack of responses from the fellows and international members. It is possible that the use of EOS risk calculator is either falsely high in our report as the response rate may be higher from the providers using the EOS risk calculator or falsely low due to a low response rate. A non-response bias may have had an impact on both providers' willingness to endorse calculator use and the outcomes related to clinical practice. It is possible that the survey respondents may be using the EOS calculator for all neonates born at > 34 weeks of gestation as recommended by the authors of the EOS calculator and not for only infants born to mothers with chorioamnionitis. We cannot accurately determine how many providers would have endorsed EOS calculator use in a situation where maternal chorioamnionitis was not present.

In conclusion, our prospective cross-sectional quantitative survey indicates that a large number of providers are using the neonatal EOS risk calculator for the management of neonates born to mothers with chorioamnionitis. In spite of concerns about the performance of the EOS risk calculator and the use of manpower and resources to implement it, the use of EOS risk calculator is increasing. Despite a clear guideline from the COFN, a large number of practitioners treat healthy-appearing neonates born to mothers with chorioamnionitis with a prolonged course of antibiotics solely for abnormal CBC and CRP results even if the blood culture is negative. A better strategy is needed to safely limit the sepsis evaluation and the use of broad-spectrum antibiotics in neonates born to mothers with chorioamnionitis. The COFN and the CDC should provide clear guidance to interpret abnormal CBC and CRP tests in neonates born to mothers with chorioamnionitis if empiric antibiotic is already initiated.

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Table 1

Survey questionnaire

Please read the case and provide answers based on your current practice
You are caring for a full-term ($39^{3/7}$ wk of gestation) neonate boy. The neonate was admitted to your unit because of a diagnosis of chorioamnionitis (based on maternal fever of 38.6°C) 5 h prior to the delivery. The mother was colonized with GBS, her membranes were ruptured for 16 h with clear fluid, and she received ampicillin and gentamicin 4 h prior to the delivery. The neonate was born via NSVD with Apgar scores of 8 and 9 at 1 and 5 min. After delivery room care, the asymptomatic neonate was admitted to the NICU. A blood culture was drawn on admission and antibiotics (ampicillin and gentamicin) were started
The results of a CBC and CRP at 12 h of age are as follows: WBC 24.3, Hb/Hct 16.8/57.4, Plt 267, IT ratio 0.43. *CRP 2.7 mg/dL (laboratory reference < 1.0 mg/dL). The neonate remains asymptomatic
Do you use the “early-onset sepsis calculator” (https://neonatalsepsiscalculator.kaiserpermanente.org/) in your practice?
A. Yes
B. No
Would you consider repeating the CBC and CRP at 24 HOL?
A. Yes
B. No
Will you perform a lumbar puncture for this patient at 12 HOL?
A. Yes
B. No
You repeated the laboratories at 24 hours and here are the new values: WBC 20, IT ratio 0.3 and CRP 4.0. The neonate remains asymptomatic and feeding well, and the blood culture is negative so far. Would you perform LP at this time?
A. Yes
B. No
How long would you consider treating this asymptomatic infant with abnormal laboratories at 12 ± 24 HOL and negative blood culture (normal CSF if performed)?
A. 48 h if blood culture is negative
B. 72 h if blood culture is negative
C. Will decide based on laboratories at 48 h of life
D. 5 d
E. 7 d
Would you repeat laboratories at 48 HOL regardless of the duration of antibiotic therapy for this infant?
A. Yes
B. No
General questions:
1. How long have you been in practice?
A. 0–2 y
B. 3–5 y
C. 6–10 y
D. 11 –15 y
E. More than 15 y
2. What is the level of your NICU?
A. Level I
B. Level II

C. Level III
D. Level IV
3. Is your institution a teaching hospital (medical school or residency program)?
a. Yes
b. No
4. Region of the United States
A. Northeast
B. West
C. South
D. Midwest

Abbreviations: CBC, complete blood count; CRP, C-reactive protein; CSF, cerebrospinal fluid; GBS, group B streptococcus; Hb/Hct, hemoglobin/hematocrit; HOL, hours of life; IT, immature to total neutrophil; NICU, neonatal intensive care unit; NSVD, normal spontaneous vaginal delivery; Plt, platelet; WBC, white blood cell.

Table 2

Distribution of clinicians using the EOS risk calculator for infants born to mothers with clinical chorioamnionitis

All		**169/682 (24.8)**
Region	Northeast	46/201 (23)
	South	34/173[a] (20)
	Midwest	47/168 (28)
	West	39/125[a] (31)
Level of NICU	Level I	0/4 (0)
	Level II	8/57[b] (14)
	Level III	106/403[b] (26)
	Level IV	55/216 (25)
Teaching	Teaching hospital	109/430 (25)
	Nonteaching hospital	59/247 (24)
Years in practice	5 or less	36/152 (24)
	>5	106/452 (23)

Abbreviations: EOS, early-onset sepsis; NICU, neonatal intensive care unit.

Note: *n* (%).

[a] $p = 0.03$, west versus south.

[b] $p = 0.03$, level II versus level III.

Table 3

Distribution of responses on the duration of treatment of an asymptomatic infant born to mothers with chorioamnionitis with abnormal laboratories at 12 ± 24 hours of life, negative blood culture, and normal CSF studies if performed (n = 682)

Duration of treatment	Number of respondents, *n* (%)
48 h	335 (49)
72 h	44 (6.4)
5 d	38 (5.6)
7 d	149 (21.8)
Decision based on laboratory findings at 48 h	112 (16.4)
No response	4 (0.6)

Abbreviation: CSF, cerebrospinal fluid.

Table 4

The distribution of clinicians who will not stop antibiotics at 48 to 72 hours of age in asymptomatic neonates born to mothers with chorioamnionitis if CBC and CRP tests are abnormal, even if the blood culture is negative

All		299/682 (44)
Region	Northeast	87/203 (43)
	South	73/173 (42)
	Midwest	78/167 (47)
	West	48/125 (38)
Level of NICU	Level I	1/4(25%)
	Level II	28/58 (48)
	Level III	186/400 (46)
	Level IV	84/216 (39)
Teaching	Teaching hospital	185/429 (43)
	Nonteaching hospital	111/246 (45)
Years in practice	5 or less	76/152 (50)
	>5	189/450 (42)

Abbreviations: CBC, complete blood count; CRP, C-reactive protein; NICU, neonatal intensive care unit.

Note: *n* (%).