Early-onset sepsis: a predictive model based on maternal risk factors

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Purpose of review
Neonatal early-onset sepsis (EOS) is a very low-incidence, but potentially fatal condition among term and late preterm newborns. EOS algorithms based on risk-factor threshold values result in evaluation and empiric antibiotic treatment of large numbers of uninfected newborns, leading to unnecessary antibiotic exposures and maternal/infant separation. Ideally, risk stratification should be quantitative, employ information conserving strategies, and be readily transferable to modern comprehensive electronic medical records.

Recent findings
We performed a case–control study of infants born at or above 34 weeks' gestation with blood culture-proven EOS. We defined the relationship of established predictors to the risk of EOS, then used multivariate analyses and split validation to develop a predictive model using objective data. The model provides an estimation of sepsis risk that can identify the same proportion of EOS cases by evaluating fewer infants, as compared with algorithms based on subjective diagnoses and cut-off values for continuous predictors.

Summary
An alternative approach to EOS risk assessment based only on objective data could decrease the number of infants evaluated and empirically treated for EOS, compared with currently recommended algorithms. Prospective evaluation is needed to determine the accuracy and safety of using the sepsis risk model to guide clinical decision-making.

Keywords
Bayesian statistics, intrapartum antibiotics, neonatal early-onset sepsis, neonatal infection, risk prediction

INTRODUCTION

Neonatal early-onset sepsis (EOS) is diagnosed as blood or cerebrospinal fluid culture-proven bacterial infection of the newborn occurring primarily in the first 72 h of life. Advances in obstetrical and neonatal care have decreased the incidence of EOS in the United States. In 1996, just before the Centers for Disease Control and Prevention (CDC) recommended intrapartum antibiotic prophylaxis (IAP) to prevent EOS caused by group B *Streptococcus* (GBS), the overall incidence of EOS was 3–4 cases/1000 live births [1–4]. Currently, the overall US incidence of EOS has declined to approximately 0.8 cases/1000 live births [5▪▪]. Infants born at less than 29 weeks' gestation suffer EOS roughly 20 times more frequently than term infants, and 30–50% of very premature infants with EOS die of the infection. In contrast, the incidence of EOS among infants born at or above 34 weeks' gestation is 0.4–0.6 cases/1000 births, with associated mortality of 0–3%. Fewer than two-thirds of term infants with EOS require neonatal intensive care, and 20% are cared for in normal newborn nursery settings [6▪]. Striking differences in the incidence, microbiology, and clinical consequences of EOS among term and very premature infants, as well as expected differences in physiologic instability, mandate that EOS be considered separately among these groups.

Faced with a very low-incidence, but potentially high-consequence, illness, neonatal clinicians must

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KEY POINTS

- Standard algorithms for the evaluation of term and late preterm infants for early-onset sepsis are based on risk-factor threshold values that waste information and dichotomize newborns as 'at risk' or 'not at risk.'
- An accurate multivariate predictive model of early-onset sepsis risk has been developed for infants born at or above 34 weeks' gestation, using only objective clinical data available at the time of birth.
- On the basis of five predictors, the model uses multivariate computational methods to represent the full value of each predictor as well as to account for interactions between predictors, and performs better than standard algorithms.
- The model incorporates a Bayesian approach by starting with the rate of EOS within the population of infants born at or above 34 weeks' gestation, and provides an infant-specific, updated prior probability of EOS which could be combined with clinical status and laboratory values to guide evaluation and treatment decisions.

regularly confront the following questions after newborn birth. Am I worried that this baby in front of me has EOS? Am I worried enough to evaluate the baby for EOS? Should I just observe, or obtain laboratory tests? Am I so worried that I should administer empiric antibiotics? Clinicians must make these decisions knowing that each means (in most care settings) separating the mother and newborn for hours or days. When the newborn has unequivocal signs of illness, clinicians need no guidance to decide whether to initiate empiric antibiotics and intensive care. However, because some infants with EOS may be initially asymptomatic, and many infants with and without EOS have equivocal and/or transient signs of illness, decisions to initiate an evaluation and begin empiric antibiotic therapy among infants are less clear. In this review, we will briefly summarize the epidemiologic studies that identified EOS risk factors in infants at or above 34 weeks' gestation, and review the content and impact of published algorithms that aid the clinician in making these EOS decisions. We will then describe an alternate approach to EOS risk assessment that takes a Bayesian perspective and uses objective data to provide a quantitative estimate of risk to inform clinical decision-making.

RISK FACTORS FOR EARLY-ONSET SEPSIS

It has been recognized since the late 1950s that bacterial EOS originates in the antenatal/intrapartum period [7–8]. The pathogenesis of EOS is that of ascending colonization of the maternal genital tract and amniotic cavity with maternal gastrointestinal and genitourinary flora, leading to infection of the uterus, placenta and umbilical cord (chorioamnionitis and funisitis) with subsequent or coincident colonization and infection of the fetus. Multiple studies have assessed the role of specific intrapartum maternal and neonatal characteristics in predicting risk of neonatal EOS. In addition to the strong predictor of low gestational age, identified clinical risk factors include maternal rectovaginal colonization with GBS, prolonged duration of rupture of membranes (ROM), and specific obstetrical practices (such as membrane stripping and frequent internal examinations) [2,9–13]. The obstetrical diagnosis of chorioamnionitis, and the individual signs that make up this clinical diagnosis (maternal intrapartum fever, uterine tenderness, fetal tachycardia, maternal tachycardia, and foul-smelling or purulent amniotic fluid) [12,14▪,15] may signal the presence of maternal inflammation and infection that increase neonatal risk of EOS. The administration of IAP decreases the risk of both GBS-specific and all-cause EOS [4,11,16], although the efficacy is greater when given as true prophylaxis (based on maternal antepartum GBS screening), as opposed to administering IAP for other risk factors [9].

NEONATAL EARLY-ONSET SEPSIS RISK ALGORITHMS

CDC guidelines for the prevention of perinatal GBS disease were initially published in 1996, revised in 2002, and most recently revised in November 2010 [1,14▪,17]. Each version provides recommendations for the evaluation of newborns for all-bacterial cause EOS, including evaluation criteria for the lowest-risk category of infants, asymptomatic infants born at or near term gestation. The American Academy of Pediatrics Committee on the Fetus and Newborn (COFN) recently issued guidelines for the evaluation and empiric treatment of infants at risk for EOS [18▪]. The CDC 2010 and COFN 2012 guidelines are both based on critical review of substantial literature, and seek to ensure infant safety. They both address the evaluation of infants born to women with chorioamnionitis, and those born to women who did not receive indicated GBS prophylaxis. Table 1 summarizes the respective recommendations for late preterm and term infants. Both sources refer to the risk presented by 'maternal chorioamnionitis' without offering a standard definition of this clinical diagnosis. From a practical standpoint, many obstetricians and neonatal clinicians use this term interchangeably with

Table 1. Comparison of standard early-onset sepsis risk assessment recommendations for asymptomatic term and late preterm infants

	CDC 2010 [14▪]	COFN 2012 [18▪]
Components of EOS Evaluation	Blood culture at birth and CBC with WBC differential and platelet count (at birth and/or at 6–12 h of life)	Blood culture at birth; CBC with WBC differential and platelet counts, at 6–12 h of life, (±) CRP
Course of care: Maternal Chorioamnionitis	EOS evaluation and empiric antibiotic therapy for undefined duration pending blood culture results	EOS evaluation and empiric antibiotic therapy pending blood culture results for (a) minimum 48 h if laboratory data normal; (b) undefined duration if laboratory data abnormal and mother received intrapartum antibiotics
Course of care: ROM >18 h as sole risk factor	No specific recommendation	CBC/differential/platelet, at 6–12 h of life, (±) CRP; blood culture if laboratory data abnormal; observation only if laboratory data normal
Course of care: Inadequate indicated GBS IAP	EOS evaluation if infant ROM >18 h, or gestational age <37 weeks	CBC/differential/platelet, at 6–12 h of life, (±) CRP; blood culture if laboratory data abnormal; and observation only if laboratory data normal

CBC, complete blood count; CRP, c-reactive protein; EOS, early-onset sepsis; ROM, rupture of membranes; WBC, white blood cell count.

intrapartum maternal fever. The lack of precision in the term 'chorioamnionitis' presents considerable difficulty to clinicians who recognize that making this diagnosis – or not – leads to different courses of care with different potential risks and benefits. Both algorithms consider maternal intrapartum antibiotic treatment for chorioamnionitis to be a significant risk for neonatal EOS rather than a potential protective benefit. The published algorithms differ in their recommendations with regard to the evaluation of infants on the basis of inadequate GBS prophylaxis or with the single risk factor of ROM at least equal to 18 h. The variable risk associated with inadequate GBS IAP was identified in the first randomized study of the efficacy of GBS IAP [16]. In that study, the overall attack rate for GBS-specific EOS was 10.2/1000 in the absence of maternal IAP. However, when maternal colonization status was subcategorized by additional characteristics, in the absence of IAP, very different levels of risk become apparent. Among the infants born to GBS-colonized women with labors complicated by ROM more than 12 h and/or birth less than 37 weeks' gestation, the attack rate was 63/1000; among those born to women with labors complicated by maternal fever at least 37.5°C, the attack rate was 130/1000. However, for those infants born to GBS-colonized women without additional intrapartum risk factors, the attack rate was only 4.3/1000.

DEVELOPMENT OF A MULTIVARIATE PREDICTION MODEL FOR EARLY-ONSET SEPSIS

The uncertainty around the best course of care for infants born to women with inadequate IAP, or after intrapartum treatment for presumed chorioamnionitis, emphasizes the importance of multiple considerations in assessing the risk of EOS. Standard algorithms largely account for EOS risk factors in isolation, without consideration of the relative contribution of each risk factor or of interactions between them. Recently, we completed the largest case–control study of intrapartum risk factors for EOS among term and late preterm infants in the era of GBS prophylaxis [19▪▪]. The purpose of our study was to develop a multivariate model of EOS risk among term and late-preterm infants to help guide clinicians' decision to initiate EOS evaluation and empiric treatment. We did not seek to identify new predictors for EOS, but to define the quantitative and qualitative relationship of established predictors and choose those most useful to a multivariate prediction model. In developing this model, we had several goals. First, we sought to determine if a robust model could be built using only objective data that would be available at the moment of birth. Perhaps most important to clinicians, we used 'highest maternal intrapartum temperature' rather than the clinical diagnosis of chorioamnionitis. Second, we designed the model to harness the power of multivariate computational methods, to account for the interactions between individual predictors and represent the full value of each predictor. The model was not designed for manual computation, but was intended for use within electronic medical records (EMRs). Third, we wished to quantify the impact of all types and time frames of intrapartum antibiotic exposure.

To achieve our goals, we started with a birth cohort of 608 014 live births, representing all live births at or above 34 weeks' gestation occurring at 14 different California and Massachusetts hospitals

from 1995 to 2007. The time frame was chosen to reflect time periods in which GBS IAP was used at each site, with either a risk factor-based or a screening-based policy. We identified 350 cases of EOS and matched these 1 : 3 to 1063 control infants randomly selected from the birth cohort, frequency-matched by hospital site and year of birth to account for local obstetric practice and trends in EOS incidence. For statistical model development, we used split validation with a derivation data set consisting of two-thirds of the original cases and controls. We made the a-priori decision to consider the final model successfully validated if it had an area under the receiver operator characteristic (*c* statistic) more than 0.75, with good calibration as assessed by multiple metrics.

We first examined the bivariate associations of specific variables to choose the predictors to include in the multivariate model. Gestational age at delivery, maternal fever, use of epidural analgesia, prolonged ROM and intrapartum antibiotic use were strong individual predictors of infection. Intrapartum use of broad-spectrum antibiotics was more strongly associated with infection than intrapartum use of GBS-specific antibiotics; each presumably resulted from confounding by indication. In contrast, on bivariate analysis, positive GBS status was not a significant positive predictor of EOS, perhaps reflecting the role of GBS IAP. We examined the relationship of individual predictors within the case–control cohort and used bootstrapping methods to determine the relationship of these to risk within the entire study population. We found a nonlinear relationship between gestational age and EOS; risk decreased from 34–40 weeks' gestation and rose again after 40 weeks' gestation. The association of EOS with postdates delivery had not been previously identified. Examining highest maternal intrapartum temperature, we observed a slow, nearly linear increase in risk between 99.5°F (37.5 C) and 100.4°F (38.0 C) but a rapid increase in risk above that level. In contrast, we found that the relationship of EOS to time of ROM was more uniform, although capturing it mathematically required a nonintuitive transformation, as shown in Table 2.

On multivariate analysis, several differences emerge. Positive GBS status is a significant positive predictor, and all types and durations of intrapartum antibiotics are significant negative predictors. Epidural analgesia as a separate input did not improve the model, likely reflecting the interaction of this form of obstetrical anesthesia with height of maternal temperature. We chose five predictors for incorporation into the final model, and represented each in a manner that took full advantage of the information provided by each factor (Table 2). GBS status was included as a categorical variable (positive, negative or unknown) but highest maternal temperature, gestational age and duration of ROM were included as continuous variables with appropriate representation of their relationship to EOS. Incorporation of intrapartum antibiotic exposure presented us with the greatest challenge in model development. Despite our large sample size, we did not have adequate statistical power to represent all possible combinations of maternal GBS status, type of antibiotic used and duration of antibiotic in our model. After assessing the accuracy and calibration of many possible models, we decided to represent antibiotic exposure in a categorical fashion. First, we categorized antibiotics into two categories: those used primarily for GBS prophylaxis, and broad-spectrum antibiotics used when there is concern for maternal chorioamnionitis. Second, we considered antibiotics given at least 4 h prior to delivery, as required for maximally effective GBS IAP, to constitute adequate intrapartum antibiotic treatment. The intrapartum antibiotic variable in the final model, thus, has three possible values (zero for no intrapartum antibiotic; one for GBS-specific antibiotics, or broad-spectrum antibiotics given <4 h prior to delivery; or two for broad-spectrum antibiotics given ≥ 4 h prior to delivery). This assignment scheme was based on the predicted clinical efficacy (or 'value') of the type of intrapartum antibiotic if an infant is bacteremic with an EOS pathogen. No antibiotic would be predicted to have no value. GBS-specific antibiotics given at least 4 h before delivery are of full value if the infant is infected with GBS, but may be of insufficient value if infected with another (potentially ampicillin-resistant) organism. Likewise, both GBS-specific and broad-spectrum antibiotics given less than 4 h before delivery would be considered to have some, but insufficient, value. Broad-spectrum antibiotics given at least 4 h before delivery would be considered to be of most value, because these antibiotics would likely be effective against both GBS and non-GBS pathogens.

When applied to the entire data set, the final model had good discrimination (*c* statistic 0.800) and calibration (Hosmer-Lemeshow *P* value 0.142). The two most important predictors were highest antepartum temperature, which accounted for 58% of the model's predictive ability in the entire data set, and gestational age, which accounted for 17%. Application of standard EOS risk algorithms can result in evaluation of approximately 15% of term and late-preterm infants [19▪▪,20▪]. By taking full advantage of available information, we demonstrated that the multivariate model can identify as

Table 2. Components of multivariate model

Variable	Variable Type	Values
Group B *Streptococcus* status	Categorical	Negative, Positive or Unknown
Gestational age	Continuous	Exact gestational age in weeks, specified to the day (GA) and $(GA)^2$
Duration of ROM	Continuous	Transformed ROM time = [rupture of membranes time in hours + 0.05]$^{0.2}$
Highest intrapartum temperature	Continuous	Value to 0.1 °F
Intrapartum antibiotics	Categorical	Indicator variables; three mutually exclusive values:
GBS IAP: penicillin, ampicillin, clindamycin, erythromycin, cefazolin, vancomycin		No intrapartum antibiotic
Broad-spectrum: other cephalosporins; fluoroquinolone; extended spectrum beta-lactam; OR any IAP antibiotic *plus* an aminoglycoside		GBS IAP given on time or antibiotics given *not* on time
On time: first dose given ≥4 h prior to delivery		Broad-spectrum antibiotics given on time

ROM, rupture of membranes.
Reproduced from [19▪▪].

many cases of EOS as standard algorithms using cutoff values for risk factors; however, only approximately 40% as many infants will be evaluated.

A comparison of this model with the use of standard EOS risk algorithms is provided in Table 3. The multivariate approach provides several potential advantages over the use of standard algorithms. First, the model uses only objective data, relieving the neonatal and obstetrical clinician from making the diagnosis of chorioamnionitis. Second, the model takes full advantage of continuous information (such as that of maternal temperature) rather than using dichotomous approaches that waste the information provided by values above and below cut-off levels. Third, the model accounts for all forms and durations of intrapartum antibiotic exposures. Finally, the model is not meant for manual use but is computational. It provides a sepsis risk estimate, and may be accessed from a website (http://www.dor.kaiser.org/external/DORExternal/

Table 3. Comparison of standard early-onset sepsis risk algorithms and multivariate early-onset sepsis risk model

	Standard algorithms	Multivariate model
Definition of chorioamnionitis	Provide no guidance to make this clinical diagnosis. Clinicians often set local cut-off values for maternal fever of concern	Uses only objective data of highest maternal intrapartum temperature, eliminating need for clinical diagnosis. Does not dichotomize data but accounts for risk across all temperatures
ROM risk factor	Dichotomize risk, assuming no contribution of ROM <18 h	Incorporates ROM as a continuous variable, accounting for all ROM duration >0 h
Gestational age risk factor	Dichotomize risk as: birth <37 weeks – a risk; birth ≥37 weeks – not a risk	Incorporates gestational age as continuous variable from 34–43 weeks, accounting for increased risk associated with both late preterm and postdates birth
Intrapartum antibiotic consideration	Accounts only for protective value of GBS prophylaxis given >4 h prior to delivery	Accounts for protective value of all forms and durations of intrapartum antibiotic exposure
Maternal GBS status	Dichotomize risk as that associated with GBS status or that associated with chorioamnionitis	Incorporates GBS status as one variable in overall risk assessment
Risk approach	Newborn categorized as 'at risk' or 'not at risk'	Provides continuous estimation of risk, allowing clinicians to determine acceptable level of risk in different clinical settings
Adaptation to variability in EOS incidence	Do not account for EOS incidence	Multivariate regression equation intercept accounts for baseline incidence of EOS in population; this can be adjusted to local variability in EOS incidence
Clinical work flow	Manual determination by flow diagram	Computational tool that can be incorporated into an electronic medical record

EOS, early-onset sepsis; GBS, group B *Streptococcus*; ROM, rupture of membranes.

research/InfectionProbabilityCalculator.aspx), via a smart phone app (http://76.170.4.32/sepsis/) or incorporated in an EMR. If desired, the model can be adjusted for variability in local incidence of EOS when incorporating it into a local EMR.

CONCLUSION

Use of our predictive model will require neonatal clinicians to be explicit about specifying acceptable level of EOS risk in different clinical scenarios. The sepsis risk estimate is not meant to be used in isolation, but rather it should be used within a Bayesian approach. The model begins with the risk of EOS within the population of infants born at or above 34 weeks' gestation, and provides the clinician with a patient-specific, updated prior probability of EOS that can be used to determine how to proceed in evaluating and empirically treating the infant for EOS. Infant clinical status and laboratory values (if obtained) must also be considered; we are currently devising a final model for integrating infant clinical status with the sepsis risk score. By providing a continuous estimate of the individual infant's risk of EOS, rather than dichotomizing infants into 'at risk' or 'not at risk', we believe this multivariate model can form the basis of a more efficient, quantitative EOS risk stratification strategy in the era of widespread use of intrapartum antibiotic prophylaxis.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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This article describes the study performed to develop the multivariate model of EOS risk that is the subject of this review article. The supplemental information accompanying the article provides a detailed description of the statistical methods used to develop the multivariate model, including the regression equation and a method to adjust the equation intercept, for incorporation into a local electronic medical record.

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This article describes the outcomes of implementing a local algorithm for newborn EOS evaluation based on the CDC 2002 GBS prevention guidelines, at a large maternity center.