Estimating the Probability of Neonatal Early-Onset Infection on the Basis of Maternal Risk Factors

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KEY WORDS

neonatal early-onset sepsis, neonatal infection, predictors of neonatal infection, Bayesian statistics, intrapartum antibiotic prophylaxis

ABBREVIATIONS

EOS—early-onset sepsis
GBS—group B *Streptococcus*
IAP—intrapartum antibiotic prophylaxis
EMR—electronic medical record
ROM—rupture of membranes

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WHAT'S KNOWN ON THIS SUBJECT: Risk factors for neonatal early-onset sepsis are based on results of studies performed before widespread use of group B *Streptococcus* intrapartum antibiotic prophylaxis. Sepsis algorithms based on risk-factor threshold values result in antibiotic treatment of large numbers of uninfected newborns.

WHAT THIS STUDY ADDS: An accurate multivariate predictive model of sepsis risk can be developed for infants born at ≥34 weeks' gestation. This model uses only objective clinical data available at the time of birth and performs better than currently recommended algorithms.

abstract

OBJECTIVE: To develop a quantitative model to estimate the probability of neonatal early-onset bacterial infection on the basis of maternal intrapartum risk factors.

METHODS: This was a nested case-control study of infants born at ≥34 weeks' gestation at 14 California and Massachusetts hospitals from 1993 to 2007. Case-subjects had culture-confirmed bacterial infection at <72 hours; controls were randomly selected, frequency-matched 3:1 according to year and birth hospital. We performed multivariate analyses and split validation to define a predictive model based only on information available in the immediate perinatal period.

RESULTS: We identified 350 case-subjects from a cohort of 608 014 live births. Highest intrapartum maternal temperature revealed a linear relationship with risk of infection below 100.5°F, above which the risk rose rapidly. Duration of rupture of membranes revealed a steadily increasing relationship with infection risk. Increased risk was associated with both late-preterm and postterm delivery. Risk associated with maternal group B *Streptococcus* colonization is diminished in the era of group B *Streptococcus* prophylaxis. Any form of intrapartum antibiotic given >4 hours before delivery was associated with decreased risk. Our model showed good discrimination and calibration (*c* statistic = 0.800 and Hosmer-Lemeshow $P = .142$ in the entire data set).

CONCLUSIONS: A predictive model based on information available in the immediate perinatal period performs better than algorithms based on risk-factor threshold values. This model establishes a prior probability for newborn sepsis, which could be combined with neonatal physical examination and laboratory values to establish a posterior probability to guide treatment decisions. *Pediatrics* 2011;128:e1155–e1163

Early-onset sepsis (EOS) from group B *Streptococcus* (GBS) has decreased with the widespread use of intrapartum antibiotic prophylaxis (IAP), which has led to declines in the overall incidence of EOS among term and late-preterm infants.[1–4] The Centers for Disease Control and Prevention 2002 (and revised 2010) guidelines for the prevention of neonatal GBS disease provide algorithms for the evaluation of infants at risk for EOS.[5,6] These guidelines are based on the presence or absence of particular characteristics (eg, chorioamnionitis) and the use of simple cutoffs for continuous variables (eg, maternal temperature) and result in antibiotic administration to large numbers of uninfected newborns. For example, at the Brigham and Women's Hospital in Boston, Massachusetts, in 2008–2009, 8% of well-appearing infants born at >34 weeks' gestation were treated with antibiotics for risk of infection, but the incidence of EOS among those infants was only 0.42 cases per 1000 live births.[7]

In this article we describe one of the components of a study ("Sepsis and Critical Illness in Infants ≥ 34 Weeks' Gestation") that addressed the problem of ruling out sepsis in term and late-preterm infants. Confronted with a newborn having unequivocal signs of illness, clinicians do not need predictive models to decide whether to initiate antibiotics and intensive care. However, because many infants may be asymptomatic or have equivocal signs, clinicians must make 3 decisions: (1) Should a given newborn be evaluated for sepsis? (2) Is this infant's risk sufficiently high to warrant antibiotic treatment? (3) Does this infant need intensive care?

In this report we describe a model designed to address the first of these questions by using only data that would be available in automated electronic medical records (EMRs). We used a case-control design in which the case-subjects were nested within a defined population. We began with a prior probability based on the underlying population infection rate and then incorporated objective information available in the immediate perinatal period to define a posterior rate per 1000 live births.

MATERIALS AND METHODS

Study Population

The nested case-control study was approved by the institutional review boards at all participating institutions. The base population consisted of all newborns born at ≥34 weeks' gestation at 12 Kaiser Permanente Medical Care Program hospitals in northern California and Brigham and Women's Hospital and Beth Israel-Deaconess Medical Center, both in Boston, Massachusetts.

We identified cases of EOS through the microbiology laboratories' databases from January 1, 1995, through December 31, 2007, at Kaiser Permanente Medical Care Program (KPMCP) and Beth Israel-Deaconess Medical Center (BIDMC) and from January 1, 1993, through December 31, 2007, at Brigham and Women's Hospital (BWH). A screening-based approach to GBS IAP was implemented at KPMCP sites in 2002, at BWH in 1997, and at BIDMC in 1996. Case-subjects were infants born at ≥34 weeks' gestation who had a positive blood or cerebrospinal fluid culture result for a pathogenic bacterial species before 72 hours of age. Cultures that grew nonpathogenic species (eg, coagulase-negative staphylococci) were considered cases only if the treating physician considered the infant infected, as evidenced by antibiotic treatment that lasted for ≥5 days or until neonatal death. We randomly selected 3 controls per case from the total birth cohort and frequency-matched them according to birth year and hospital. Exclusion criteria included birth outside study hospitals, chromosomal abnormalities or major congenital anomalies defined by the Vermont-Oxford Network,[8] and, for controls, positive blood or cerebrospinal fluid culture results at <72 hours of age.

Data Collection

Demographic data and procedure and discharge diagnosis codes were collected for the entire birth cohort. For case-subjects and controls, data collected by individual chart review included maternal gravidity and parity; delivery mode; GBS status; duration of rupture of membranes (ROM); maternal intrapartum temperatures; presence of meconium-stained amniotic fluid, maternal hypertension, or preeclampsia; maternal intrapartum medications; and obstetric anesthesia.

Statistical Methods

We performed all analyses by using SAS (SAS Institute, Inc, Cary, NC), Stata (Stata Corp, College Station, TX), or R.[9–11] For bivariate comparisons, we used χ^2 or Fisher's exact tests for categorical variables and t tests for continuous variables. We used split validation for multivariate model development. The derivation data set consisted of 210 randomly selected cases and 659 randomly selected controls from the original data set of 350 cases and 1063 controls. We selected variables on the basis of previously published findings[12–17] and ease of extraction from an EMR (ie, the objective "highest antepartum temperature" rather than the subjective "physician diagnosis of chorioamnionitis"). We examined bivariate associations of specific variables to choose the 5 predictors included in the multivariate model. Nonparametric smoothing methods were used to incorporate continuous variables[18–20]; complete statistical methods are available in the

Supplemental Appendix. We applied the coefficients from our best model to the remaining one-third of the cases and controls (validation data set). We made an a priori decision to consider the final model successfully validated if it had an area under the receiver operator characteristic (*c* statistic) ≥ 0.75. Calibration was assessed with the Hosmer-Lemeshow *P* value. Model performance was also assessed by visual examination of observed and expected sepsis rates by risk deciles and with multiple metrics recommended by Cook.[21]

We estimated the relative contribution of individual predictors to the overall predictive value by using the differences between the log likelihood of the full model and the log likelihood of a model without each predictor.[22,23] Relative contribution was defined as the ratio of the predictor's log-likelihood difference to the sum of the model's 5 log-likelihood differences, multiplied by 100. We estimated population-based sepsis probabilities by bootstrapping the controls to create a data set that approximates what would have been observed if we had measured all variables on the entire base population.[24] We then fit our final logistic regression model to this bootstrapped data set. This is approximately equivalent to changing the intercept in our logistic regression model to reflect actual proportions of case-subjects and controls in the base population, an approach that is needed because the study design oversamples case-subjects relative to controls. We used these methods to estimate (1) the numbers of newborns who would be classified as at risk, and correctly classified as being infected, under different scenarios and (2) the risk of infection for a given combination of predictors.

RESULTS

During the study period, 608 014 live births at ≥34⁶⁄₇ weeks' gestation occurred at the study sites. We identified 350 cases of EOS (0.58 cases per 1000 live births) and 1063 controls. The annual EOS incidence at the 3 hospitals combined varied between 0.17 and 0.92 cases per 1000 (interquartile range: 0.40–0.71). The infecting organism was GBS in 53.1% of cases and *Escherichia coli* in 20.3%. Other bacteria (including *Staphylococcus aureus*, *Listeria*, enterococci, *Bacteroides*, *Klebsiella*) accounted for <5% of cases each; only 1 case of *Staphylococcus epidermidis* was included. Demographic and delivery characteristics of case-subjects and controls were similar except that case-subjects were more likely to have been born by cesarean delivery and at <37 weeks' gestation (Tables 1 and 2). Maternal GBS status was unknown for 55% of the subjects because of both the largely unknown status of the late-preterm subjects and the predominantly risk-factor–based GBS IAP strategy that was used at the Kaiser Permanente Medical Care Program sites before 2002 (Table 2). Nearly 20% of the control deliveries were exposed to some form of intrapartum antibiotic therapy (Table 2).

TABLE 1 Demographics of Base Population and Study Subjects

	Base Population (N = 608 014)	Controls (n = 1063)	Case-Subjects (n = 350)
Maternal age, mean (±SD), y	30.1 (6.0)	30.0 (6.0)	29.8 (6.6)
Maternal ethnicity, *n* (%)			
Asian	86 890 (14.3)	163 (15.3)	50 (14.3)
Black	56 604 (9.3)	87 (8.2)	35 (10.0)
Hispanic	117 285 (19.3)	222 (20.9)	66 (18.9)
White	299 989 (49.3)	521 (49.0)	165 (47.1)
Other	47 246 (7.8)	70 (6.6)	34 (9.7)
Multiple gestation, *n* (% nonsingleton)	25 314 (4.2)	35 (3.3)	6 (1.7)
Mode of delivery, *n* (%)			
Vaginal	423 204 (69.6)	841 (79.1)	199 (56.9)
Forceps/vacuum	46 335 (7.6)	15 (1.4)	13 (3.7)
Cesarean	138 475 (22.8)	207 (19.5)	138 (39.4)
Gestational age, *n* (%)			
34–36 wk	41 465 (6.8)	69 (6.5)	49 (14.0)
37–40 wk	481 566 (79.2)	847 (79.7)	235 (67.1)
≥41 wk	84 983 (14.0)	147 (13.8)	66 (18.9)

TABLE 2 Case-Subject and Control Labor and Delivery Descriptors

	Controls (n = 1063)	Case-Subjects (n = 350)
Delivery anesthesia, *n* (%)[a]		
Epidural	606 (57.0)	265 (75.7)
Spinal	96 (9.0)	23 (6.6)
Endotracheal	2 (0.2)	6 (1.7)
None	359 (33.8)	56 (16.0)
Maternal medications, *n* (%)[b]		
Antibiotics	210 (19.8)	112 (32.0)
Magnesium sulfate	24 (2.3)	29 (8.3)
None	833 (78.4)	222 (63.4)
Maternal GBS status, *n* (%)		
Positive	146 (13.7)	63 (18.0)
Negative	310 (29.2)	117 (33.4)
Unknown	607 (57.1)	170 (48.6)

[a] The number of deliveries that involved epidural anesthesia includes 52 controls and 23 cases in which a combination of epidural and spinal anesthesia were used. When analyzed as a distinct category of anesthesia, there was no significant difference between controls and cases in the use of this combined anesthesia.

[b] Four control mothers and 3 case mothers received both intrapartum antibiotics and magnesium sulfate.

Bivariate Analyses

Preterm and postterm delivery, maternal fever, use of epidural analgesia, and prolonged ROM were strong individual predictors of infection (Table 3). Positive GBS status, compared with either negative status or negative/unknown status, was not significantly associated with increased risk of EOS. In a bivariate analysis, intrapartum antibiotic exposure (of any type and duration), compared with no antibiotic exposure, was associated with a twofold increase

TABLE 3 Bivariate Analyses

Variable	Controls (n = 1063), %	Case-Subjects (n = 350), %	OR (95% CI)
Gestational age[a]			
37–40 wk	79.7	67.1	Reference
34–36 wk	6.5	14.0	2.56 (1.73–3.79)
≥41 wk	13.8	18.9	1.62 (1.17–2.24)
Duration of ROM			
<12 h	81.2	53.6	Reference
12–17.99 h	9.7	23.4	3.65 (2.61–5.11)
18–23.99 h	4.5	8.3	2.81 (1.71–4.62)
≥24 h	4.7	14.8	4.81 (3.14–7.38)
Highest maternal temperature			
<100.5°F	95.3	70.0	Reference
100.5–101.4°F	3.9	13.1	4.53 (2.91–7.04)
101.5–102.4°F	0.7	9.7	20.08 (8.80–45.84)
≥102.5°F	0.1	7.1	103.37 (13.94–766.56)
Maternal GBS status			
Negative	68.0	65.0	Reference
Positive	32.0	35.0	1.14 (0.79–1.64)
Negative/unknown	86.3	82.0	Reference
Positive	13.7	18.0	1.38 (1.00–1.91)
Maternal intrapartum antibiotics[b]			
No intrapartum antibiotic	80.2	68.0	Reference
Any antibiotic	19.8	32.0	1.91 (1.45–2.49)
GBS IAP	18.7	29.0	1.77 (1.34–2.35)
Broad-spectrum antibiotics	4.4	22.2	6.25 (4.11–9.50)
Antibiotic <4 h before delivery	37.3	63.6	Reference
Antibiotic ≥4 h before delivery	62.8	36.5	0.34 (0.21–0.55)
Delivery anesthesia[c]			
No epidural	43.0	24.3	Reference
Epidural	57.0	75.7	2.40 (1.79–3.09)

OR indicates odds ratio; CI, confidence interval.

[a] Study captured gestational age in exact weeks and days.

[b] See Table 4 for definitions of GBS IAP and broad-spectrum antibiotics.

[c] Delivery anesthesia was analyzed as the use of epidural anesthesia compared with all other deliveries that included no anesthesia or the use of a nonepidural form of anesthesia.

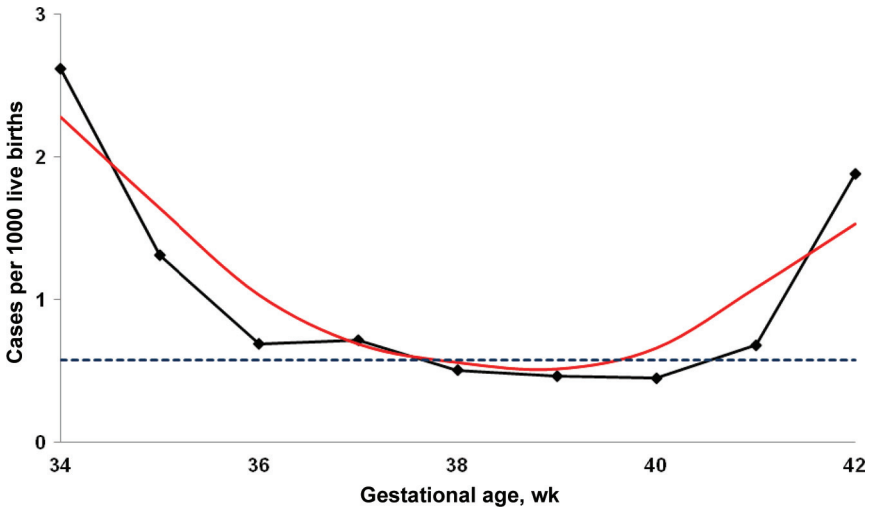

FIGURE 1

Rate of sepsis according to gestational age. For Figs 1 through 3, a data set was created by including all 350 cases and bootstrapping the 1063 controls in the total (derivation plus validation) data set up to 607 664 simulated controls, for a total of 608 014 simulated births. Shown here are the empirical sepsis rates in the bootstrap data set broken down according to weeks of gestational age. The dotted line represents the overall sepsis frequency in the base population (0.58 per 1000). The red line represents a local regression (Lowess) smooth of the relationship of gestational age to sepsis rate. See the Supplemental Appendix for full details of the statistical methods.

in risk of infection. Intrapartum use of broad-spectrum antibiotics was more strongly associated with infection than intrapartum use of GBS-specific antibiotics. These positive bivariate associations were presumably a result of confounding by indication. Any intrapartum antibiotic given ≥4 hours before delivery, however, was associated with a decreased risk of infection.

The bivariate relationships of gestational age, highest maternal intrapartum temperature, and duration of ROM with culture-proven infection are shown graphically in Figs 1 through 3. We found a nonlinear relationship with gestational age; risk decreased from 34 to 40 weeks' gestation and rose again after 40 weeks' gestation (Fig 1). We observed a slow, nearly linear increase in risk between 99.5°F and 100.4°F but a rapid increase in risk above that level (Fig 2). Infection risk also increased monotonically with increasing time of ROM (Fig 3).

Multivariate Analyses and Posterior Probabilities

Tables 4 and 5 list the components and performance of our final multivariate model. After controlling for maternal temperature, epidural analgesia was not a significant predictor in multivariate analyses and was not included in the final model. When applied to the entire data set, the final model had good discrimination (c statistic = 0.800) and calibration (Hosmer-Lemeshow P value = .142) (Table 5). The 2 most important predictors were the 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% (Table 6).

Table 7 highlights the potential application of screening strategies based on defined posterior probabilities and shows that they can be superior to approaches based on dichotomous thresholds.

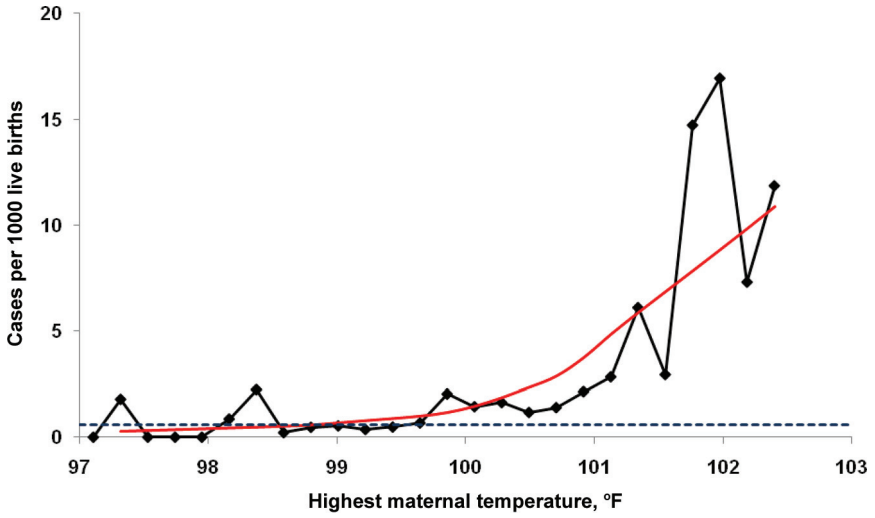

FIGURE 2

Rate of sepsis according to highest maternal intrapartum temperature. Temperature was measured to the nearest 0.1°F, including values from 97°F to 104.2°F. Values above 102.5°F were infrequent. Empirical sepsis relative frequencies were computed in the bootstrapped data set. The dotted line represents the overall sepsis frequency in the base population. The red line represents a local regression (Lowess) smooth of the relationship of temperature to sepsis rate. See the Supplemental Appendix for full details of the statistical methods.

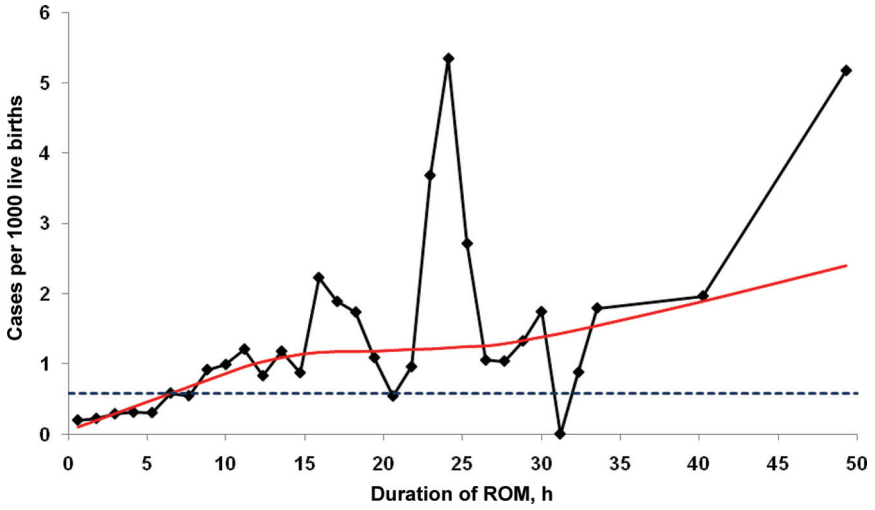

FIGURE 3

Rate of sepsis according to duration of ROM. ROM was measured to the nearest 0.1 hour and took on values from 0 to 226.4 (inclusive); ROM times of >50 hours were rare, and times between 30 and 50 hours were sparse. Empirical sepsis relative frequencies were computed in the bootstrapped data set. The dotted line represents the overall sepsis frequency in the base population. The red line represents a local regression (Lowess) smooth of the relationship of duration of ROM to sepsis rate. See the Supplemental Appendix for full details of the statistical methods.

DISCUSSION

We conducted a nested case-control study that provides a substantial improvement over previous approaches to the problem of how to rule out sepsis in term and late-preterm newborns. Our study incorporated a Bayesian approach that began with a prior probability based on the rate of sepsis in the study population. This was modified as intrapartum characteristics became available and yielded an updated prior probability of sepsis that, when combined with subsequent information (data from a newborn's clinical examination and/or laboratory evaluation), can be used to guide evaluation and treatment decisions. Our objectives were to define a multivariate predictive model with 2 attributes: (1) it would be based only on maternal data available at the moment of delivery; and (2) it would rely on objective data available in an EMR.

Use of our predictive model will require neonatal clinicians to be explicit about specifying a level of risk at which one should evaluate newborns for EOS. The clinical factors used to inform the overall risk of EOS have been based primarily on studies performed before the widespread use of GBS IAP.[12–14] Evaluations of the impact of GBS prophylaxis on term and late-preterm neonatal risk have been lacking. Centers for Disease Control and Prevention investigators completed case-control studies of all EOS in 1995–1996 and of *E coli* EOS from 1997 to 2001, but both studies included large proportions of high-risk <34-week-gestation infants.[15,16] Escobar et al[17] studied a cohort of 2785 infants with a birth weight of >2000 g evaluated for EOS during a period (1995–1996) in which IAP was administered by using a risk-based strategy. That study identified maternal fever, intrapartum antibiotic treatment, and infant clinical status as the most important factors for predicting culture-proven infection among an at-risk cohort.

This report provides clinicians with a multivariate tool to determine EOS risk among term and late-preterm infants in the era of GBS prophylaxis. It permits clinicians to incorporate key clinical factors into risk estimates. For example, the model incorporates maternal intrapartum antibiotic treatment and accounts for modification of a newborn's risk as a result of such treatment. It also takes full advantage

TABLE 4 Components of Multivariate Model

Variable	Variable Type	Value
GBS 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 = $(\text{ROM time in hours} + 0.05)^{0.2}$
Highest intrapartum temperature	Continuous	Value to 0.1°F
Intrapartum antibiotics	Categorical	Indicator variables; 3 mutually exclusive values: (1) no intrapartum antibiotic; (2) GBS IAP given on time or antibiotics given not on time; (3) broad-spectrum antibiotics given on time[a]
GBS IAP: penicillin, ampicillin, clindamycin, erythromycin, cefazolin, vancomycin		
Broad-spectrum antibiotics: other cephalosporins, fluoroquinolone, extended spectrum β-lactam, or any IAP antibiotic plus an aminoglycoside		
On time: first dose given ≥4 h before delivery		

[a] Antibiotic grouping refers to predicted efficacy (or "value") of the type of intrapartum antibiotic if the infant is bacteremic with an EOS pathogen. No antibiotic would be predicted to have no value. GBS-specific antibiotics given >4 hours before delivery are of full value if the infant is infected with GBS but of possibly/likely insufficient value if infected with another organism. Likewise, both GBS-specific and broad-spectrum antibiotics given <4 hours before delivery would be considered to have some but insufficient value. Broad-spectrum antibiotics given ≥4 hours before delivery would be considered to be of full value, because these antibiotics would treat GBS and non-GBS pathogens.

TABLE 5 Multivariate Model for EOS Based on Maternal Predictors

Variable	Adjusted OR (95% CI)[a]		
Gestational age	0.001 (0.0001–0.014)		
Gestational age squared	1.09 (1.05–1.13)		
GBS carrier status			
Negative	Reference		
Positive	1.78 (1.11–2.85)		
Unknown	1.04 (0.76–1.44)		
Duration of ROM	3.41 (2.23–5.20)		
Highest intrapartum temperature	2.38 (2.05–2.77)		
Intrapartum antibiotic treatment			
None	Reference		
GBS IAP given on time or any antibiotic not given on time	0.35 (0.23–0.53)		
Broad-spectrum antibiotics given on time	0.31 (0.13–0.71)		
	Derivation	Validation	Entire
c^{2b} statistic	0.807	0.794	0.800
Hosmer-Lemeshow *P* value	.284	.349	.142

OR indicates odds ratio; CI, confidence interval.

[a] Adjusted odds ratios shown are for the model applied to the entire data set.

[b] The c^2 statistic is the area under the receiver operator characteristic curve.

TABLE 6 Relative Contribution of Predictors to Multivariate Model

Predictor[a]	Data Set, %		
	Derivation	Validation	Entire
Gestational age	10.7	26.5	16.7
GBS status	2.0	3.2	2.3
ROM time	14.8	9.3	12.6
Highest intrapartum temperature	62.5	50.1	58.4
Intrapartum antibiotics treatment	10.0	10.9	10.0

[a] Refers to either individual predictors (eg, highest intrapartum temperature) or all predictors in a group (eg, gestational age + gestational age squared or all the antibiotic variables listed in Table 1).

of available information by not using simple cutoff values for 3 continuous variables (fever, ROM time, and gestational age). The relationship of maternal temperature to risk of sepsis (Fig 2) reveals the disadvantage of relying on cutoff values: although the graph suggests that a cutoff value of 101°F defines infants at highest risk of infection, this approach ignores the fact that a fever of 102.5°F is associated with 4 times the risk of a fever of 101°F. Our study also accounts for the complex ways in which risk is modified by intrapartum antibiotic use (Tables 4 and 5), and our results show the importance of controlling for the presence of multiple risk factors and confounding by indication. Bivariate analysis of broad-spectrum antibiotic exposure revealed that this exposure defines infants at increased risk of EOS, but multivariate modeling demonstrates the protective effect of this type of intrapartum antibiotic therapy, given on time, when other relevant factors are considered. Multivariate analyses revealed that the timing of intrapartum antibiotic exposure relative to delivery is important in the prevention of culture-proven sepsis regardless of the type of antibiotic or the reason for administration. These findings support a similar protective effect of both GBS prophylaxis and broad-spectrum antibiotics on all forms of EOS, which is consistent with results of pre–GBS-IAP era studies of the effect of intrapartum antibiotic treatment for chorioamnionitis on neonates of all gestational ages.[25]

By taking full advantage of available information, our multivariate model can significantly decrease the number of infants evaluated for EOS while identifying similar numbers of cases compared with current recommended strategies (Table 7). Use of individual risk-factor threshold values results in the evaluation of variable proportions of the base population and identifies only 15% to 30% of sepsis cases. Combining all the cutoff methods flags nearly 17% of the base population as being at higher risk but identifies only 47% of sepsis cases. Use of a

TABLE 7 Comparison of Threshold Probability Approach to Individual Predictor Cutoffs When Applied to the Entire Newborn Population

Risk Factor	Prevalence, %	Infected Infants Identified, %
Highest intrapartum temperature > 100.4°F	4.73	30.0
Highest intrapartum temperature > 101.4°F	0.76	16.7
ROM time ≥ 18 h	8.66	23.1
ROM time ≥ 24 h	4.33	14.3
Highest intrapartum temperature > 100.4°F and/or ROM ≥ 18 h and/or Broad-spectrum antibiotics and/or GBS prophylaxis-specific antibiotics < 4 h	16.56	46.6
Non-GBS intrapartum antibiotics or GBS prophylaxis-specific antibiotics < 4 h	8.40	24.9
Posterior rate per 1000 live births		
Posterior rate ≥ 0.4	9.1	50.6
Posterior rate ≥ 0.5	6.1	44.9
Posterior rate ≥ 0.6	4.2	39.4
Posterior rate ≥ 1.0	1.8	24.3
Posterior rate ≥ 1.5	0.9	18.0

posterior-rate threshold per 1000 live births of 0.5 (a level of risk equal to the sepsis rate among infants born at 38–40 weeks' gestation) identifies the same proportion of cases within only 6% of the base population. Using this posterior probability subdivides the base population (sepsis rate: 0.58 per 1000 live births) into 2 subpopulations: 1 that is relatively small (6%) with a relatively high risk (4.2 in 1000) and 1 that is larger (94%) with a much lower risk (0.34 in 1000). Protocols for these 2 subpopulations could be different and might permit clinicians to make decisions that are more closely tailored to individual patient risk. The advantages of safely evaluating fewer infants include not only decreased health care expenditures but also the social benefits of decreasing separation of mothers and newborns for sepsis evaluation and treatment and health benefits that might be attributed to exposing fewer uninfected infants to antibiotic treatment.

Our model also provides information on changes in risk that might inform both obstetric and neonatal clinical decisions. For example, for an infant born at 39 weeks' gestation to a GBS-positive mother with a highest intrapartum temperature of 98.6°F and ROM time of 10 hours who did not receive GBS IAP, the posterior rate of sepsis is ~0.3 per 1000 live births. If this scenario is modified to include a maternal temperature of 101.3°F, the posterior rate is increased to 3 per 1000. In contrast, an infant born at 34 weeks' gestation to a GBS-unknown mother with a temperature of 102.3°F and ROM time of 10 hours and no intrapartum antibiotic exposure has a posterior rate of 56 per 1000 live births. Currently, consideration would be given to evaluation of all these infants without recognition of their 170-fold difference in risk. Our model also reveals the relative benefit of intrapartum antibiotic administration. In the examples cited here, the posterior rate of sepsis per 1000 live births is decreased to 0.10 (term, afebrile, GBS-positive), 0.9 (same mother febrile to 101.3°F), and 18 (preterm, febrile to 102.3°F, GBS-unknown) by the administration of appropriate intrapartum antibiotic therapy.

Our model is not intended for manual calculation but would be generated within the EMR. To ensure that this would be a practical clinical tool, we incorporated objective data that would be available at the time of delivery. The use of computer-based predictive models to aid in clinical neonatal decision-making was illustrated by Tyson et al,[26] who developed a Web-based calculator to predict outcome of very low gestational age infants before birth on the basis of a few user-input variables. Optimally, our model would be embedded in the EMR with electronic capture of the variables and use of a local prevalence of EOS, but it could also be incorporated into a Web-based calculator based on clinician inputs that use the prior probability of sepsis from our study. Either way, the risk score could be combined with infant clinical status and laboratory data to make decisions regarding evaluation for infection and initiation of empiric antibiotic treatment. It must be emphasized, however, that this Bayesian approach will require users to define a range for posterior probability based on acceptable level of risk. The level of risk that mandates an evaluation is not just a scientific decision but also an ethical and practical one. Individual institutions will need to assess their local care structure and resources to make this decision.

Although our study is, to our knowledge, the largest case-control study of EOS performed in the era of GBS IAP, it is limited by an insufficient sample size to generate stable models of all possible combinations of GBS-carriage status, type of antibiotic treatment, and time of treatment. The time frame required to identify cases for adequate statistical power resulted in an analysis that spanned the risk- and screening-based approaches to GBS IAP. This might be viewed as a study limitation, but it resulted in an analysis applicable to a broad range of situations. It should also be noted that because epidural use causes fever in ~20% of women,[27,28] the predictive value of low-grade fever

might differ on the basis of the prevalence of epidural use.

A significant strength of our study is the use of 14 study sites that provided for diversity of race and ethnicity and for variation in obstetric care between sites. Finally, we emphasize that newborn clinical status played no role in the predictive model. However, we are working on another model, and our early results indicate that both at birth and at 2 hours of life, ~85% of the case-subjects in the study were either well-appearing or mildly symptomatic (data not shown), exactly the infants for whom sepsis risk management is most challenging.

CONCLUSIONS

Using only objective data available at the time of birth, we have developed a predictive model of sepsis risk among infants born at ≥34 weeks' gestation. Use of this model in an EMR can establish a prior probability of infection at the time of birth, which can aid the clinician in subsequent decisions regarding neonatal management and safely decrease the number of infants evaluated for infection.

The multivariate model of sepsis risk reported in this article has been incorporated into a sepsis risk calculator that will provide a predicted probability of sepsis based on user-provided inputs. This calculator can be accessed at https://extapps.kaiser.org/escobar/nis3sepsisriskatbirth.xls.

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REFERENCES

1. Moore MR, Schrag SJ, Schuchat A. Effects of intrapartum antimicrobial prophylaxis for prevention of group-B-streptococcal disease on the incidence and ecology of early-onset neonatal sepsis. *Lancet Infect Dis*. 2003;3(4):201–213
2. Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG. Seventy-five years of neonatal sepsis at Yale: 1928–2003. *Pediatrics*. 2005; 116(3):595–602
3. Phares CR, Lynfield R, Farley MM. Epidemiology of invasive group B streptococcal disease in the United States, 1999–2005. *JAMA*. 2008;299(17):2056–2065
4. Puopolo KM, Eichenwald EC. No change in the incidence of ampicillin-resistant neonatal early onset sepsis over 18 Years. *Pediatrics*. 2010;125(5). Available at: www.pediatrics.org/cgi/content/full/125/5/e1031
5. Schrag S, Gorwitz R, Fultz-Butts K, Schuchat A. Prevention of perinatal group B streptococcal disease. *MMWR Recomm Rep*. 2002; 51(RR-11):1–22
6. Verani JR, McGee L, Schrag SJ; Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention. Prevention of perinatal group B streptococcal disease. Revised Guidelines from CDC, 2010. *MMWR Recomm Rep*. 2010;59(RR-10): 1–36
7. Mukhopadhyay S, Eichenwald EC, Puopolo KM. Impact of neonatal sepsis evaluation on asymptomatic infants born at ≥35 weeks' gestation. Presented at: American Pediatric Society and the Society for Pediatric Research; May 4, 2010; Vancouver, British Columbia, Canada
8. Appendix C: birth defect codes. In: Vermont Oxford Manual of Operations. Release 13.2. Available at: www.vtoxford.org/tools/2009ManualofOperationswithindex13_2.pdf. Accessed March 2, 2010
9. *SAS (Statistical Analysis Software)* [computer program]. Version 6. Carey, NC: SAS Institute; 1989
10. *Stata Statistical Software* [computer program]. Release 9. College Station, TX: Stata Corp LP; 2005
11. The R Project for Statistical Computing. Available at: www.r-project.org. Accessed April 6, 2011
12. Schuchat A, Oxtoby M, Cochi S, et al. Population-based risk factors for neonatal group B streptococcal disease: results of a cohort study in metropolitan Atlanta. *J Infect Dis*. 1990;162(3):672–677
13. Schuchat A, Deaver-Robinson K, Plikaytis BD, Zangwill KM, Mohle-Boetani J, Wenger JD. Multistate case-control study of maternal risk factors for neonatal group B streptococcal disease. *Pediatr Infect Dis J*. 1994; 13(7):623–629
14. Benitz WE, Gould JB, Druzin ML. Risk factors for early-onset group B streptococcal sepsis: estimation of odds ratios by critical literature review. *Pediatrics*. 1999;103(6). Available at: www.pediatrics.org/cgi/content/full/103/6/e77
15. Schuchat A, Zywicki SS, Dinsmoor MJ, et al. Risk factors and opportunities for prevention of early-onset neonatal sepsis: a multicenter case-control study. *Pediatrics*. 2000; 105(1 pt 1):21–26
16. Schrag SJ, Hadler JL, Arnold KE, Martell-Cleary P, Reingold A, Schuchat A. Risk factors for invasive, early-onset *Escherichia coli* infections in the era of widespread intrapartum antibiotic use. *Pediatrics*. 2006; 118(2):570–576
17. Escobar GJ, Li DK, Armstrong MA, et al. Neonatal sepsis workups in babies ≥2000 grams at birth: a population-based study. *Pediatrics*. 2000;106(2 pt 1):256–263
18. Cleveland WS. Robust locally weighted regression and smoothing scatterplots. *J Am Stat Assoc*. 1979;74(368):829–836
19. Cleveland WS. LOWESS: a program for smoothing scatterplots by robust locally weighted regression. *Am Stat*. 1981;35:54
20. Cleveland WS, Devlin SJ. Locally-weighted regression: an approach to regression analysis by local fitting. *J Am Stat Assoc*. 1988;83(403):596–610
21. Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. *Circulation*. 2007;115(7):928–935
22. Render ML, Kim HM, Welsh DE, et al. Automated intensive care unit risk adjustment: results from a National Veterans Affairs study. *Crit Care Med*. 2003;31(6):1638–1646
23. Escobar G, Greene J, Scheirer P, Gardner M, Draper D, Kipnis P. Risk adjusting hospital inpatient mortality using automated inpatient, outpatient, and laboratory databases. *Med Care*. 2008;46(3):232–239
24. Efron B, Tibshirani RJ. *An Introduction to the Bootstrap*. New York, NY: Chapman & Hall; 1993

25. Benitz WE, Gould JB, Druzin ML. Antimicrobial prevention of early-onset group B streptococcal sepsis: estimates of risk reduction based on a critical literature review. *Pediatrics*. 1999;103(6). Available at: www.pediatrics.org/cgi/content/full/103/6/e78
26. Tyson JE, Parikh NA, Langer J, Green C, Higgins RD; National Institute of Child Health and Human Development Neonatal Research Network. Intensive care for extreme prematurity: moving beyond gestational age. *N Engl J Med*. 2008;358(16):1672–1681
27. Lieberman E, Lang JM, Frigoletto F Jr, Richardson DK, Ringer SA, Cohen A. Epidural analgesia, intrapartum fever, and neonatal sepsis evaluation. *Pediatrics*. 1997;99(3):415–419
28. Riley LE, Celi AC, Onderdonk AB, et al. Association of epidural-related fever and noninfectious inflammation in term labor. *Obstet Gynecol*. 2011;117(3):588–595