JAMA Pediatrics | Original Investigation

A Quantitative, Risk-Based Approach to the Management of Neonatal Early-Onset Sepsis

Michael W. Kuzniewicz, MD, MPH; Karen M. Puopolo, MD, PhD; Allen Fischer, MD; Eileen M. Walsh, RN, MPH; Sherian Li, MS; Thomas B. Newman, MD, MPH; Patricia Kipnis, PhD; Gabriel J. Escobar, MD

IMPORTANCE Current algorithms for management of neonatal early-onset sepsis (EOS) result in medical intervention for large numbers of uninfected infants. We developed multivariable prediction models for estimating the risk of EOS among late preterm and term infants based on objective data available at birth and the newborn's clinical status.

OBJECTIVES To examine the effect of neonatal EOS risk prediction models on sepsis evaluations and antibiotic use and assess their safety in a large integrated health care system.

DESIGN, SETTING, AND PARTICIPANTS The study cohort includes 204 485 infants born at 35 weeks' gestation or later at a Kaiser Permanente Northern California hospital from January 1, 2010, through December 31, 2015. The study compared 3 periods when EOS management was based on (1) national recommended guidelines (baseline period [January 1, 2010, through November 31, 2012]), (2) multivariable estimates of sepsis risk at birth (learning period [December 1, 2012, through June 30, 2014]), and (3) the multivariable risk estimate combined with the infant's clinical condition in the first 24 hours after birth (EOS calculator period [July 1, 2014, through December 31, 2015]).

MAIN OUTCOMES AND MEASURES The primary outcome was antibiotic administration in the first 24 hours. Secondary outcomes included blood culture use, antibiotic administration between 24 and 72 hours, clinical outcomes, and readmissions for EOS.

RESULTS The study cohort included 204 485 infants born at 35 weeks' gestation or later: 95 343 in the baseline period (mean [SD] age, 39.4 [1.3] weeks; 46 651 male [51.0%]; 37 007 white, non-Hispanic [38.8%]), 52 881 in the learning period (mean [SD] age, 39.3 [1.3] weeks; 27 067 male [51.2%]; 20 175 white, non-Hispanic [38.2%]), and 56 261 in the EOS calculator period (mean [SD] age, 39.4 [1.3] weeks; 28 575 male [50.8%]; 20 484 white, non-Hispanic [36.4%]). In a comparison of the baseline period with the EOS calculator period, blood culture use decreased from 14.5% to 4.9% (adjusted difference, −7.7%; 95% CI, −13.1% to −2.4%). Empirical antibiotic administration in the first 24 hours decreased from 5.0% to 2.6% (adjusted difference, −1.8; 95% CI, −2.4% to −1.3%). No increase in antibiotic use occurred between 24 and 72 hours after birth; use decreased from 0.5% to 0.4% (adjusted difference, 0.0%; 95% CI, −0.1% to 0.2%). The incidence of culture-confirmed EOS was similar during the 3 periods (0.03% in the baseline period, 0.03% in the learning period, and 0.02% in the EOS calculator period). Readmissions for EOS (within 7 days of birth) were rare in all periods (5.2 per 100 000 births in the baseline period, 1.9 per 100 000 births in the learning period, and 5.3 per 100 000 births in the EOS calculator period) and did not differ statistically (P = .70). Incidence of adverse clinical outcomes, including need for inotropes, mechanical ventilation, meningitis, and death, was unchanged after introduction of the EOS calculator.

CONCLUSIONS AND RELEVANCE Clinical care algorithms based on individual infant estimates of EOS risk derived from a multivariable risk prediction model reduced the proportion of newborns undergoing laboratory testing and receiving empirical antibiotic treatment without apparent adverse effects.

JAMA Pediatr. 2017;171(4):365-371. doi:10.1001/jamapediatrics.2016.4678
Published online February 20, 2017.

Supplemental content

Author Affiliations: Perinatal Research Unit, Division of Research, Kaiser Permanente Northern California, Oakland (Kuzniewicz, Walsh, Li, Escobar); Department of Pediatrics, University of California, San Francisco (Kuzniewicz, Newman); The Permanente Medical Group, Oakland, California (Kuzniewicz, Fischer, Escobar); Newborn Care at Pennsylvania Hospital, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (Puopolo); Perelman School of Medicine, University of Pennsylvania, Philadelphia (Puopolo); Systems Research Initiative, Division of Research, Kaiser Permanente Northern California, Oakland (Kipnis, Escobar).

Corresponding Author: Michael W. Kuzniewicz, MD, MPH, Perinatal Research Unit, Division of Research, Kaiser Permanente Northern California, 2000 Broadway Ave, Oakland, CA 94612 (michael.w.kuzniewicz@kp.org).

Copyright 2017 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a SUNY Stony Brook User on 08/17/2021

Neonatal early-onset sepsis (EOS) is defined as invasive bacterial infection of the blood and/or cerebrospinal fluid (CSF) that occurs in the first week after birth. The pathogenesis is primarily ascending colonization of the maternal genital tract and uterine compartment with normal maternal gastrointestinal and genitourinary tract bacterial flora, resulting in subsequent colonization and infection of the fetus or newborn. Often EOS presents with nonspecific signs (eg, tachypnea) that are also associated with normal transition to extrauterine life. In addition, EOS may result in severe systemic illness and even death in 3% to 4% of infected infants.[1,2]

The Centers for Disease Control and Prevention (CDC),[3] the American Congress of Obstetricians and Gynecologists,[4,5] and the American Academy of Pediatrics[6] provide guidelines for the prevention of neonatal group B *Streptococcus* (GBS), including recommendations for intrapartum antibiotic prophylaxis and algorithms for evaluation and treatment of at-risk infants. These guidelines are based on epidemiologic data obtained before the widespread obstetric use of intrapartum antibiotic prophylaxis (when EOS incidence was 5- to 10-fold higher than currently observed).[7-11] These guidelines result in a large percentage (15%-20%) of term and late preterm infants being evaluated for sepsis, with 5% to 8% receiving empirical antibiotics.[12,13] Persistent high rates of evaluation and treatment contrast with the decreasing incidence of EOS (0.3-0.8 cases per 1000 births).[12-14]

Using a Bayesian approach and a base population of 608 014 newborns, we developed 2 linked prediction models for EOS. The first model establishes a newborn's prior probability of EOS based on gestational age, highest maternal antepartum temperature, GBS carriage status, duration of rupture of membranes, and the nature and timing of intrapartum antibiotic administration.[15] The second model quantifies how the baseline risk is modified by the infant's clinical examination.[16] We instantiated these models with an online calculator (kp.org\eoscalc).[13] The key elements of the calculator are summarized in eFigure 1 in the Supplement. We made this calculator available to physicians at Kaiser Permanente Northern California (KPNC), an integrated health care system in Oakland, California, and instructed clinicians on its use. In this report, we describe the effect of this calculator on the rate of blood cultures in neonates, antibiotic use, and adverse outcomes.

Key Points

Question Can the use of a predictive model to estimate risk of early-onset sepsis safely decrease the proportion of newborns evaluated by blood culture and empirically treated with antibiotics?

Findings We compared evaluations by blood culture, antibiotic administration, and readmissions for early-onset sepsis before and after clinical implementation of a predictive model for early-onset sepsis. Evaluations by blood culture and empirical antibiotic administration decreased significantly without any significant increase in the rate of readmissions for early-onset sepsis.

Meaning Clinical care based on a predictive model reduces the proportion of newborns evaluated and empirically treated for early-onset sepsis without apparent adverse effects.

Methods

Study Population and Setting

The study cohort included 204 485 infants born at 35 weeks' gestation or later at a KPNC hospital from January 1, 2010, through December 31, 2015. Although we developed prediction models using populations that included infants born at 34 weeks' gestation, we excluded those infants because they are routinely admitted to the neonatal intensive care unit and experience a higher level of monitoring. At the KPNC, all inpatient and outpatient care is tracked through a common medical record number. If care outside the KPNC was required for extracorporeal membrane oxygenation (ECMO), we captured data on repatriation to the KPNC or death. Births occur at 14 hospitals. Infants born at a KPNC hospital are covered under the mother's insurance for a minimum of 30 days, regardless of the infant's insurance status. The KPNC Institutional Review Board approved this study and waived informed consent because this was a data-only study.

Intervention and Study Periods

The baseline period was defined as January 1, 2010, through November 31, 2012, when clinical care was informed by the CDC GBS guidelines.[3-5] During the learning period (December 1, 2012, through June 30, 2014), the EOS calculator based only on maternal data was made available for clinical use, but no guidance was given with respect to incorporation of the newborn clinical presentation or intervention thresholds, permitting staff to familiarize themselves with the calculator and probability of EOS at birth. In the EOS calculator period (July 1, 2014, through December 31, 2015), the newborn's clinical presentation (well, equivocal, and clinically ill) was incorporated into the risk prediction, and recommendations based on the probability of EOS were included in the calculator output. The categories of clinical presentation are defined at http://kp.org/eoscalc and in eFigure 1 in the Supplement. Blood cultures were recommended if the EOS risk was 1 or more per 1000 live births and empirical antibiotics if the EOS risk was 3 or more per 1000 live births.[13]

Outcomes

Our primary outcome was antibiotic administration in the first 24 hours. Secondary outcomes included blood culture use in the first 24 hours, antibiotic administration between 24 and 72 hours, and number of days of antibiotic use (antibiotic days) per 100 live births. We obtained data on antibiotics from the electronic medication administration record and ascertained blood and CSF cultures from the KPNC laboratory database. Antibiotic days were tabulated as the number of calendar days the infant received at least 1 dose of intravenous antibiotics. To evaluate safety, we assessed readmissions for EOS and clinical outcomes in our EOS cases. We defined EOS as blood or CSF culture-confirmed infection with a pathogenic bacterial species that occurred from birth through 7 days of age. We reviewed the medical records of all EOS cases to determine the

Copyright 2017 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a SUNY Stony Brook User on 08/17/2021

Table 1. Infant and Maternal Characteristics by Study Period[a]

Characteristic	Study Period			P Value[b]
	Baseline (n = 95 543)	Learning Period (n = 52 881)	EOS Calculator (n = 56 261)	
Birth weight, mean (SD), g	3394 (498)	3393 (496)	3385 (497)	.006
Gestational age, mean (SD), wk	39.4 (1.3)	39.3 (1.3)	39.4 (1.3)	<.001
Male	46 651 (51.0)	27 067 (51.2)	28 575 (50.8)	.40
SGA infants (<10th percentile)	4773 (5.0)	2539 (4.8)	3065 (5.5)	<.001
GA<38 wk	1280 (13.4)	7393 (14.0)	7523 (13.4)	.004
Race/ethnicity				
White, non-Hispanic	37 007 (38.8)	20 175 (38.2)	20 494 (36.4)	<.001
Asian	21 320 (22.4)	12 140 (23.0)	12 907 (23.0)	
African American	6893 (7.2)	3405 (6.4)	3701 (6.6)	
Hispanic	21 928 (23.0)	11 112 (21.0)	12 244 (21.8)	
Other or unknown	8195 (8.6)	6049 (11.4)	6915 (12.3)	
Cesarean delivery	24 835 (26.1)	13 872 (26.2)	14 504 (25.8)	.20
GBS status				
Positive	21 475 (22.5)	12 369 (23.4)	12 363 (22.0)	<.001
Unknown	6015 (6.3)	2018 (3.8)	2276 (4.1)	
Maternal temperature ≥38°C	4282 (4.5)	2325 (4.4)	2442 (4.3)	.40
ROM≥18 h	15 048 (15.8)	8666 (16.4)	9609 (17.1)	<.001
Maternal antibiotic use	20 695 (21.7)	11 690 (22.1)	12 147 (21.6)	.09
EOS	24 (0.03)	15 (0.03)	12 (0.02)	.80

Abbreviations: EOS, early-onset sepsis; GA, gestational age; GBS, group B *Streptococcus*; ROM, rupture of membranes; SGA, small for gestational age.

[a] Data are presented as number (percentage) of infants unless otherwise indicated.

[b] Analysis of variance or χ^2 test.

infant's clinical presentation, severity of illness, and outcomes until hospital discharge. We assessed severity of illness in terms of need for mechanical ventilation or inotrope medications, the presence of meningitis defined by CSF culture and/or cell count, or death due to sepsis.

Statistical Analysis

We compared infant and maternal characteristics across the periods using the χ^2, Fisher exact, and analysis of variance tests, as appropriate. We displayed monthly rates of testing and treatment using statistical process control charts. The baseline period was used to calculate the control limits, ±3 SDs of the mean. We estimated the effect of the intervention using an interrupted time series design[17,18] with segmented regression models controlling for preintervention levels, trends, and other confounders (ie, other events that occurred around the same time as the intervention and that potentially influenced the outcome). We measured time in months (from 1 to 72). Segmented regression models fit a least squares regression line to separate segments of time when certain events took place and assume a linear association between time and the outcome in each segment.[19] This method is an appropriate means of analysis for this study because we have a clear differentiation of the baseline, learning, and intervention periods; we have short-term outcomes that were expected to change relatively quickly after an intervention is implemented; and sequential measures of the outcomes are available before and after the intervention. For each outcome, we tested for a possible change in the intercept and slope in the learning period and EOS calculator period while controlling for confounding covariates. The models we fit are described in eFigure 2 in the Supplement. We explored the effects on time-varying confounders, such as seasonality and population characteristics, including monthly percentage of male infants, cesarean delivery, rupture of membranes time of 18 hours or longer, preterm infants, intrapartum antibiotics, GBS positivity, small for gestational age infants, and African American infants. We retained covariates in the final model if they were significant at a 2-sided $P < .05$. Finally, we assessed for autocorrelation in each of the time series by examining the plot of residuals and the partial autocorrelation function. We used autoregressive integrated moving average models to adjust for autocorrelation when it was present.[20] We compared readmissions for culture-positive sepsis or meningitis, differences in EOS organism, symptoms, and infant outcomes by using the χ^2 or Fisher exact test, as appropriate.

Results

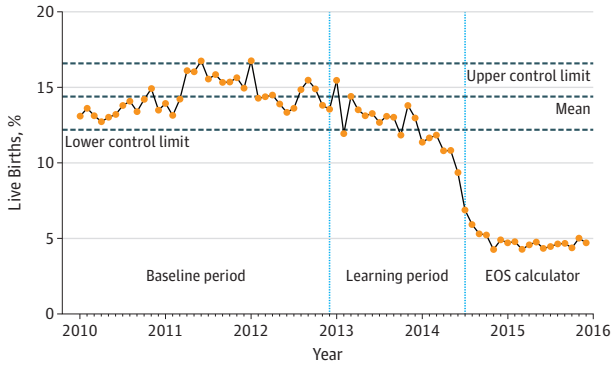
The study cohort included 204 485 infants born at 35 weeks' gestation or later: 95 343 in the baseline period (mean [SD] age, 39.4 [1.3] weeks; 46 651 male [51.0%]; 37 007 white, non-Hispanic [38.8%]), 52 881 in the learning period (mean [SD] age, 39.3 [1.3] weeks; 27 067 male [51.2%]; 20 175 white, non-Hispanic [38.2%]), and 56 261 in the EOS calculator period (mean [SD] age, 39.4 [1.3] weeks; 28 575 male [50.8%]; 20 484 white, non-Hispanic [36.4%]). Characteristics of the infants born in these 3 periods were similar (**Table 1**), with small but statistically significant demographic differences among the periods. The incidence of culture-confirmed EOS was not statistically different across periods.

Figure 1 and **Figure 2** show the monthly rates of infants undergoing a sepsis evaluation with a blood culture and re-

Copyright 2017 American Medical Association. All rights reserved.

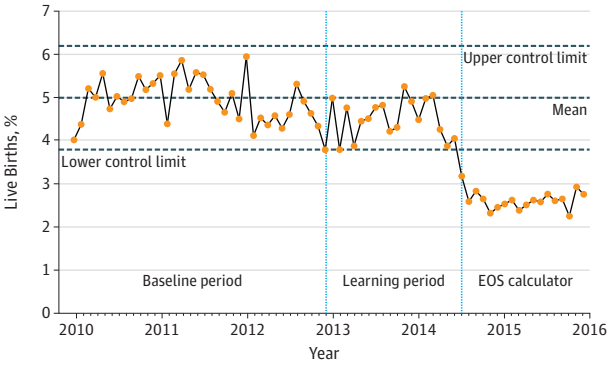
Downloaded From: https://jamanetwork.com/ by a SUNY Stony Brook User on 08/17/2021

Figure 1. Monthly Early-Onset Sepsis (EOS) Evaluation Rate



Monthly percentage of infants born at 35 weeks' gestation or later undergoing EOS evaluation with a blood culture performed in the first 24 hours of life.

Figure 2. Monthly Antibiotic Treatment Rate



Monthly percentage of infants born at 35 weeks' gestation or later receiving intravenous antibiotic therapy in the first 24 hours of life. EOS indicates early-onset sepsis.

Table 2. Comparison of Sepsis Evaluation and Antibiotic Use in the Baseline and EOS Calculator Periods[a]

Variable	Study Period		Absolute Difference, % (95% CI)	
	Baseline (n = 95 543)	EOS Calculator (n = 56 261)	Unadjusted	Adjusted
Blood culture in first 24 h	13 797 (14.5)	2741 (4.9)	−9.6 (−9.3 to −9.9)	−7.7 (−13.1 to −2.4)
Antibiotic use in first 24 h	4741 (5.0)	1482 (2.6)	−2.3 (−2.1 to −2.5)	−1.8 (−2.4 to −1.3)
Antibiotic use at >24 to 72 h	485 (0.5)	216 (0.4)	−0.1 (−0.05 to 0.2)	0.05 (−0.1 to 0.2)
Antibiotic use days per 100 infants	16.0	8.5	−7.6 (−6.7 to −8.5)	−3.3 (−6.1 to −0.5)

Abbreviations: EOS, early-onset sepsis; GBS, group B *Streptococcus*.

[a] Data are presented as number (percentage) of infants and absolute difference (95% CI) except for antibiotic days per 100 infants, which is days of antibiotic use.

ceiving intravenous antibiotics in the first 24 hours after birth. In a comparison of the baseline period and the EOS calculator period, blood culture use decreased from 14.5% to 4.9%; the adjusted difference (change in level from the interrupted time series analysis) was −7.7% (95% CI, −13.1% to −2.4%) (**Table 2**). Empirical antibiotic administration in the first 24 hours decreased from 5.0% to 2.6% (adjusted difference, −1.8%; 95% CI, −2.4% to −1.3%). There was no evidence of an increase in antibiotic use between 24 and 72 hours after birth because use decreased from 0.5% to 0.4% (adjusted difference, 0.05%; 95% CI, −0.12% to 0.22%). Antibiotic days per 100 births also decreased from 16.0 to 8.5 days (adjusted difference, −3.3 days; 95% CI, −6.1 to −0.5 days). The learning period was not statistically different from the baseline period in the segmented regression models. The time trend (slope) during the EOS period and learning period did not significantly differ from the baseline period in any of the final models.

We addressed 2 potential adverse effects of decreasing rates of newborn sepsis evaluation and empirical antibiotics: delayed treatment of infants with EOS presenting with more severe clinical illness and increases in hospital readmissions for EOS after hospital discharge. We reviewed all cases of EOS during the study. No statistically significant differences existed among the study periods in the proportion of cases caused by GBS and *Escherichia coli*, the timing of case identification, or the presence of symptoms (**Table 3**).

Sepsis-associated severity of illness, as assessed by use of mechanical ventilation, inotrope medications, meningitis, or death, did not differ among the study periods. The infant who died during the learning period had pulmonary hypertension and respiratory failure and underwent immediate treatment with antibiotics, mechanical ventilation, and ECMO. The infant who died during the EOS calculator period was born with severe hypoxic-ischemic encephalopathy and underwent immediate treatment with antibiotics, mechanical ventilation, inotropic agents, therapeutic hypothermia, and ECMO.

Of the 12 infants with EOS born during the EOS calculator period, 6 were symptomatic at birth and empirically treated with antibiotics. Five infants were well-appearing at birth; each developed symptoms during the birth hospitalization that prompted evaluation and antibiotic therapy. Only 1 infant would have met the criteria for sepsis evaluation under the CDC guidelines. The infant was born to a mother who was GBS positive with fever (temperature to 38.0°C) who did not receive antibiotics. The infant was well at birth with an EOS risk of 0.15 per 1000 births but developed tachypnea, prompting a blood culture at approximately 36 hours of life. The infant's respiratory rate normalized, and the infant was discharged home. The blood culture eventually yielded *E coli,* prompting readmission. Blood and CSF culture samples obtained before antibiotic therapy were sterile. One infant never developed symptoms but would have been empirically administered antibiotics under the CDC guidelines. The infant was born to a GBS-positive mother with fever (temperature to 39.1°C) who received antibiotics after delivery. This infant had an estimated EOS risk of 2.3 per 1000 births, and per the calculator recommendations, a blood sample was obtained for culture at birth. Antibiotic treatment was started when the culture yielded GBS.

Copyright 2017 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a SUNY Stony Brook User on 08/17/2021

Table 3. Clinical Characteristics and Outcomes of Infants With EOS by Study Period

Variable	No. (%) of Infants by Study Period[a]		
	Baseline (n = 24)	Learning Period (n = 15)	EOS Calculator (n = 12)
Organism			
GBS	11 (45.8)	6 (40.0)	3 (25.0)
Escherichia coli	5 (20.8)	6 (40.0)	5 (41.7)
Other	8 (33.3)	3 (20.0)	4 (33.3)
Symptomatic at birth	12 (50.0)	8 (53.3)	6 (50.0)
Developed symptoms before discharge	4 (16.7)	4 (26.7)	5 (41.7)
Never symptomatic	8 (33.3)	3 (20.0)	1 (8.3)
Mechanical ventilation	0	2 (13.3)	1 (8.3)[b]
Inotropic agents	2 (8.3)	1 (6.7)[c]	1 (8.3)[b]
CSF culture positive	0	0	0
Elevated CSF WBC count	1 (4.2)	2 (13.3)	2 (16.7)[d]
Death	0	1 (6.7)[c]	1 (8.3)[b]

Abbreviations: CSF, cerebrospinal fluid; EOS, early-onset sepsis; GBS, group B *Streptococcus*; WBC, white blood cell.

[a] $P > .05$ for all comparisons between the baseline and EOS calculator periods.

[b] Severe *hypoxic-ischemic encephalopathy* at birth, blood culture positive for GBS, and transferred for cooling and extracorporeal membrane oxygenation.

[c] Persistent pulmonary hypertension of the newborn and respiratory failure at birth, blood culture positive for *E coli*, and transferred for extracorporeal membrane oxygenation.

[d] Antibiotic treatment started at birth and blood culture positive for *E coli*.

Additional blood and CSF culture samples obtained before antibiotic treatment were sterile. Given the lack of significant symptoms and clearing of blood cultures before antibiotic therapy, both cases may have represented transient bacteremia rather than true sepsis. The manner in which all EOS cases presented, timing of blood cultures and antibiotic treatment, and EOS risk after birth are provided in the eTable in the Supplement.

Readmissions in the first 7 days after birth with a positive blood culture or CSF culture result were rare in all periods. During the baseline period, 5 infants (5.2 per 100 000 births) were readmitted; during the learning period, 1 infant was readmitted (1.9 per 100 000 births); and during the EOS calculator period, 3 infants were readmitted (5.3 per 100 000 births) ($P = .70$ for difference in proportions across periods). The infants readmitted during the EOS calculator period were all term, asymptomatic during their initial hospitalization, and born to afebrile mothers with rupture of membranes time ranging from 3 to 14 hours. All presented to the emergency department with fever. To capture cases of culture-negative sepsis, we also ascertained infants readmitted within 7 days of birth who received 5 days or more of antibiotic therapy despite sterile blood and/or CSF cultures. The only such case occurred during the baseline period.

Discussion

Although the use of predictive analytics is garnering increased attention in the scientific literature,[21,22] use of patient-specific, multivariable sepsis risk estimates to guide the care of newborns represents a significant shift from current recommended practice in neonatology. Our work provides prospective validation of the efficiency and safety of this approach.

The CDC EOS recommendations were based on epidemiologic findings that preceded widespread implementation of intrapartum antibiotic prophylaxis. These recommendations have been highly effective in reducing the burden of EOS.[3,23] The guidelines suggest empirical administration of antibiotics for all newborns with a maternal diagnosis of chorioamnionitis, regardless of the infant's clinical condition. Chorioamnionitis technically describes inflammation of the chorionic and amniotic fetal membranes but has been widely applied to any intrapartum temperature of 38.0°C or higher. In our approach, we use the highest maternal temperature, modeled as a log-linear relationship with EOS. A recent National Institutes of Health–sponsored conference of experts in obstetric and neonatal care highlighted the shortcomings of current approaches based on a clinical diagnosis of chorioamnionitis and urged the use of alternate approaches, including our EOS calculator.[24] Our results indicate that EOS risk can be accurately and safely assessed without using a clinical diagnosis of chorioamnionitis.

A multicenter analysis examined whether infant clinical appearance alone could be used to rule out EOS among infants born to mothers with a clinical diagnosis of chorioamnionitis.[25] That analysis found that EOS can occur among infants with initially reassuring clinical status. Our study found that only 50% of infants with EOS were symptomatic at birth. These findings underscore the importance of our approach, incorporating multiple risk factors and the evolving clinical status in the first day of life. The CDC recommends sepsis evaluations for newborns who are clinically ill (a term that is not defined).[3] Our approach adds clarity by categorizing physiologic disturbances by duration and severity.

The goal of all existing approaches to neonatal sepsis risk assessment is newborn safety. In this study, we assessed safety by measuring the incidence of EOS, use of antibiotics at 24 to 72 hours of age, proportion of infants with EOS who experienced critical illness or death, and incidence of EOS readmissions across the 3 study periods. We were concerned that if antibiotic administration immediately after birth prevents low-level bacteremia from progressing to clinical illness and/or detectable bacteremia, a decrease in early antibiotic use could result in higher rates of EOS. We did not find any difference in the overall rate of EOS across the study periods. Another concern was that if the EOS calculator failed to appropriately identify asymptomatic infants destined to later develop symptomatic EOS, infants would become ill later in the birth hospitalization, have more severe illness, or present with illness

Copyright 2017 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a SUNY Stony Brook User on 08/17/2021

after discharge. We did not find any difference in use of antibiotics at 24 to 72 hours of age that would indicate a skew toward later symptomatic EOS. We also did not find any difference in the proportion of infants with EOS who required intensive care or who died of EOS. Finally, we found no change in the low baseline rate of readmissions for culture-confirmed or culture-negative EOS in the first 7 days after birth.

In the EOS calculator period, antibiotic treatment was initiated in 2 infants with bacteremia later than the time recommended by the CDC. Neither infant had clinical sepsis, and additional blood cultures were sterile before the administration of antibiotics. A proportion of infants with EOS in each period were well-appearing at birth and presented with clinical signs of illness later in the birth hospitalization. Every approach to EOS risk assessment involves the decision to offer only clinical observation at a certain level of predicted risk. Prior approaches have not been explicit about this decision. The calculator approach requires clinicians to explicitly identify the level of predicted risk at which specific actions (clinical observation, laboratory testing, or empirical antibiotics) will be taken.[13]

Limitations

Because newborn safety is of paramount importance, limitations of our study must be emphasized. First, rare serious events may not be detected: although we report a cohort of more than 200 000 births, the population incidence of EOS is low, and the incidence of additional hospitalization for EOS is another 10-fold lower. Larger studies are warranted to evaluate the safety of delaying antibiotic treatment until infants become symptomatic or a blood culture test result becomes positive. Nonetheless, in our cohort, no adverse events were seen, suggesting that even if there is a negative effect, it is uncommon and would need to be weighed against the negative effects of sepsis evaluations and antibiotic exposure. Second, not all cases of EOS can be predicted by *any* risk factor–based strategy. Previous studies[16,26,27] have found that GBS-specific EOS continues to occur in infants born to mothers who screen falsely negative for GBS, without other intrapartum risk factors for EOS, underscoring the need for clinical observation as part of any EOS strategy. Third, our study was conducted in an integrated health care system with high rates of prenatal care and comprehensive postdischarge care. The prior probability of EOS in lower-resource settings may differ from those in the KPNC; however, the EOS calculator adjusts for this by allowing for the input of the baseline EOS incidence in the target population to appropriately increase EOS risk predictions. Although some birth hospitals may lack the KPNC outpatient follow-up infrastructure, our data indicate that readmission for EOS in the first week of life is rare. Non-KPNC hospitals have adopted variations of the EOS calculator and have also reported reductions in antibiotic use.[28,29] Fourth, because this study evaluated the implementation of the EOS calculator in infants born at 35 weeks' gestation or later, the results are not applicable to infants born earlier.

Conclusions

Antibiotic treatment has risks and benefits, and the administration of antibiotics to uninfected patients means that they only assume the risks. As more studies reveal the association between early antibiotic exposure and diseases in childhood, such as asthma,[30-35] autoimmune disorders,[36-38] and obesity,[39-42] it is important to improve antibiotic stewardship, limiting unnecessary antibiotic exposure. Furthermore, no antibiotic treatment is not the same as no care. Our approach substitutes close clinical observation, increased frequency of infant vital sign ascertainment, and parental education for wider use of empirical antibiotic treatment.[13] If adopting our approach, individual centers must assess local care structures and resources and outpatient supports, including the presence of reliable home caregivers and access to pediatric care. Although our models account for differences in the local prior probability of infection, centers with poor prenatal care (and low rates of GBS screening), lack of pediatric follow-up, and/or poor social support after discharge may justify setting different risk thresholds for clinical interventions.

Experts in neonatology have questioned the need for high rates of empirical antibiotic treatment among term and late preterm newborns.[24,43,44] Our study suggests that antibiotic stewardship can safely begin at birth.

ARTICLE INFORMATION

Accepted for Publication: November 28, 2016.

Published Online: February 20, 2017. doi:10.1001/jamapediatrics.2016.4678

Author Contributions: Dr Kuzniewicz had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Kuzniewicz, Puopolo, Newman, Escobar.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Kuzniewicz, Puopolo, Escobar.
Critical revision of the manuscript for important intellectual content: Puopolo, Fischer, Walsh, Li, Newman, Kipnis, Escobar.
Statistical analysis: Kuzniewicz, Li, Kipnis, Escobar.
Obtained funding: Newman, Escobar.
Administrative, technical, or material support: Kuzniewicz, Fischer, Walsh, Escobar.
Study supervision: Escobar.

Conflict of Interest Disclosures: None reported.

REFERENCES

1. Weston EJ, Pondo T, Lewis MM, et al. The burden of invasive early-onset neonatal sepsis in the United States, 2005-2008. *Pediatr Infect Dis J*. 2011;30(11):937-941.

2. Stoll BJ, Hansen NI, Sánchez PJ, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. *Pediatrics*. 2011;127(5):817-826.

3. Verani JR, McGee L, Schrag SJ; Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC). Prevention of perinatal group B streptococcal disease–revised guidelines from CDC, 2010. *MMWR Recomm Rep*. 2010;59(RR-10):1-36.

4. American College of Obstetricians and Gynecologists Committee on Obstetric Practice. ACOG Committee Opinion No. 485: prevention of early-onset group B streptococcal disease in newborns. *Obstet Gynecol*. 2011;117(4):1019-1027.

5. Schrag S, Gorwitz R, Fultz-Butts K, Schuchat A. Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC. *MMWR Recomm Rep*. 2002;51(RR-11):1-22.

Copyright 2017 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a SUNY Stony Brook User on 08/17/2021

6. Brady MT, Polin RA. Prevention and management of infants with suspected or proven neonatal sepsis. *Pediatrics*. 2013;132(1):166-168.

7. Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG. Seventy-five years of neonatal sepsis at Yale: 1928-2003. *Pediatrics*. 2005;116(3):595-602.

8. 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.

9. Phares CR, Lynfield R, Farley MM, et al; Active Bacterial Core surveillance/Emerging Infections Program Network. Epidemiology of invasive group B streptococcal disease in the United States, 1999-2005. *JAMA*. 2008;299(17):2056-2065.

10. Puopolo KM, Eichenwald EC. No change in the incidence of ampicillin-resistant, neonatal, early-onset sepsis over 18 years. *Pediatrics*. 2010;125(5):e1031-e1038.

11. CDC. Clinical Overview of Group B Strept (GBS). 2015; http://www.cdc.gov/groupbstrep/clinicians/clinical-overview.html. Accessed May 1, 2015, 2015.

12. Mukhopadhyay S, Eichenwald EC, Puopolo KM. Neonatal early-onset sepsis evaluations among well-appearing infants: projected impact of changes in CDC GBS guidelines. *J Perinatol*. 2013;33(3):198-205.

13. Kuzniewicz MW, Walsh EM, Li S, Fischer A, Escobar GJ. Development and implementation of an early-onset sepsis calculator to guide antibiotic management in late preterm and term neonates. *Jt Comm J Qual Patient Saf*. 2016;42(5):232-239.

14. Mukhopadhyay S, Dukhovny D, Mao W, Eichenwald EC, Puopolo KM. 2010 perinatal GBS prevention guideline and resource utilization. *Pediatrics*. 2014;133(2):196-203.

15. Puopolo KM, Draper D, Wi S, et al. Estimating the probability of neonatal early-onset infection on the basis of maternal risk factors. *Pediatrics*. 2011;128(5):e1155-e1163.

16. Escobar GJ, Puopolo KM, Wi S, et al. Stratification of risk of early-onset sepsis in newborns ≥ 34 weeks' gestation. *Pediatrics*. 2014;133(1):30-36.

17. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther*. 2002;27(4):299-309.

18. Kontopantelis E, Doran T, Springate DA, Buchan I, Reeves D. Regression based quasi-experimental approach when randomisation is not an option: interrupted time series analysis. *BMJ*. 2015;350:h2750.

19. Lopez Bernal J, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial [published online June 9, 2016]. *Int J Epidemiol*. doi:10.1093/ije/dyw098

20. Nelson BK. Statistical methodology, V: time series analysis using autoregressive integrated moving average (ARIMA) models. *Acad Emerg Med*. 1998;5(7):739-744.

21. Bates DW, Saria S, Ohno-Machado L, Shah A, Escobar G. Big data in health care: using analytics to identify and manage high-risk and high-cost patients. *Health Aff (Millwood)*. 2014;33(7):1123-1131.

22. Parikh RB, Kakad M, Bates DW. Integrating predictive analytics into high-value care: the dawn of precision delivery. *JAMA*. 2016;315(7):651-652.

23. Centers for Disease Control and Prevention. Active Bacterial Core Surveillance Report, Emerging Infections Program Network, Group B Streptococcus. 2014. http://www.cdc.gov/abcs/reportsfindings/survreports/gbs14.pdf. Accessed February 17, 2016.

24. Higgins RD, Saade G, Polin RA, et al; Chorioamnionitis Workshop Participants. Evaluation and management of women and newborns with a maternal diagnosis of chorioamnionitis: summary of a workshop. *Obstet Gynecol*. 2016;127(3):426-436.

25. Wortham JM, Hansen NI, Schrag SJ, et al; Eunice Kennedy Shriver NICHD Neonatal Research Network. Chorioamnionitis and culture-confirmed, early-onset neonatal infections. *Pediatrics*. 2016;137(1):1-11.

26. Puopolo KM, Madoff LC, Eichenwald EC. Early-onset group B streptococcal disease in the era of maternal screening. *Pediatrics*. 2005;115(5):1240-1246.

27. Van Dyke MK, Phares CR, Lynfield R, et al. Evaluation of universal antenatal screening for group B streptococcus. *N Engl J Med*. 2009;360(25):2626-2636.

28. Kerste M, Corver J, Sonnevelt MC, et al. Application of sepsis calculator in newborns with suspected infection. *J Matern Fetal Neonatal Med*. 2016;29(23):3860-3865.

29. Shakib J, Buchi K, Smith E, Young PC. Management of newborns born to mothers with chorioamnionitis: is it time for a kinder, gentler approach? *Acad Pediatr*. 2015;15(3):340-344.

30. Örtqvist AK, Lundholm C, Kieler H, et al. Antibiotics in fetal and early life and subsequent childhood asthma: nationwide population based study with sibling analysis. *BMJ*. 2014;349:g6979.

31. Sun W, Svendsen ER, Karmaus WJ, Kuehr J, Forster J. Early-life antibiotic use is associated with wheezing among children with high atopic risk: a prospective European study. *J Asthma*. 2015;52(7):647-652.

32. Wegienka G, Zoratti E, Johnson CC. The role of the early-life environment in the development of allergic disease. *Immunol Allergy Clin North Am*. 2015;35(1):1-17.

33. Arrieta MC, Finlay B. The intestinal microbiota and allergic asthma. *J Infect*. 2014;69(suppl 1):S53-S55.

34. Alm B, Erdes L, Möllborg P, et al. Neonatal antibiotic treatment is a risk factor for early wheezing. *Pediatrics*. 2008;121(4):697-702.

35. Russell SL, Gold MJ, Hartmann M, et al. Early life antibiotic-driven changes in microbiota enhance susceptibility to allergic asthma. *EMBO Rep*. 2012;13(5):440-447.

36. Hviid A, Svanström H, Frisch M. Antibiotic use and inflammatory bowel diseases in childhood. *Gut*. 2011;60(1):49-54.

37. Kronman MP, Zaoutis TE, Haynes K, Feng R, Coffin SE. Antibiotic exposure and IBD development among children: a population-based cohort study. *Pediatrics*. 2012;130(4):e794-e803.

38. Shaw SY, Blanchard JF, Bernstein CN. Association between the use of antibiotics in the first year of life and pediatric inflammatory bowel disease. *Am J Gastroenterol*. 2010;105(12):2687-2692.

39. Ajslev TA, Andersen CS, Gamborg M, Sørensen TI, Jess T. Childhood overweight after establishment of the gut microbiota: the role of delivery mode, pre-pregnancy weight and early administration of antibiotics. *Int J Obes (Lond)*. 2011;35(4):522-529.

40. Bailey LC, Forrest CB, Zhang P, Richards TM, Livshits A, DeRusso PA. Association of antibiotics in infancy with early childhood obesity. *JAMA Pediatr*. 2014;168(11):1063-1069.

41. Murphy R, Stewart AW, Braithwaite I, Beasley R, Hancox RJ, Mitchell EA; ISAAC Phase Three Study Group. Antibiotic treatment during infancy and increased body mass index in boys: an international cross-sectional study. *Int J Obes (Lond)*. 2014;38(8):1115-1119.

42. Saari A, Virta LJ, Sankilampi U, Dunkel L, Saxen H. Antibiotic exposure in infancy and risk of being overweight in the first 24 months of life. *Pediatrics*. 2015;135(4):617-626.

43. Cotten CM. Antibiotic stewardship: reassessment of guidelines for management of neonatal sepsis. *Clin Perinatol*. 2015;42(1):195-206, x. x.

44. Benitz WE, Wynn JL, Polin RA. Reappraisal of guidelines for management of neonates with suspected early-onset sepsis. *J Pediatr*. 2015;166(4):1070-1074.

Copyright 2017 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a SUNY Stony Brook User on 08/17/2021