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# Risk Assessment in Neonatal Early-Onset Sepsis

**Sagori Mukhopadhyay**[1,4] and **Karen M. Puopolo**[1,2,3,4]

[1]Division of Newborn Medicine, Children's Hospital Boston, 300 Longwood Avenue, Boston, MA 02115

[2]Channing Laboratory 181 Longwood Avenue, Boston, MA 02115

[3]Department of Newborn Medicine, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115

[4]Harvard Medical School, 25 Shattuck Street Boston, MA 02115

## Abstract

The incidence of neonatal early-onset sepsis has declined with the widespread use of intrapartum antibiotic therapies, yet early-onset sepsis remains a potentially fatal condition, particularly among very low-birth weight infants. Clinical signs of neonatal infection are non-specific and may be absent in the immediate postnatal period. Maternal and infant clinical characteristics, as well as infant laboratory values, have been used to identify newborns at risk, and to administer empiric antibiotic therapy to prevent progression to more severe illness. Such approaches result in the evaluation of approximately 15% of asymptomatic term and late preterm infants and of nearly all preterm infants. The development of multivariate predictive models may provide more accurate methods of identifying newborns at highest risk and allow for more limited newborn antibiotic exposures.

## Introduction

Neonatal early-onset sepsis (EOS) is defined as blood or cerebrospinal fluid culture-proven bacterial infection of the newborn occurring in the first 7 days of life. Among very-low birth weight infants (VLBW, or birth weight < 1500 grams) EOS is restricted to infection occurring in the first 72 hours of life, as the microbiology of and risk factors for infection among these infants reflect nosocomial rather than perinatal exposures after this time period. Advances in obstetrical and neonatal care have decreased the incidence of EOS. The overall incidence of EOS in the United States was 3-4 cases per 1000 live births just prior to the first Centers for Disease Control and Prevention (CDC) guideline recommending the use of intrapartum antibiotic prophylaxis (IAP) to prevent perinatal Group B *Streptococcus* (GBS) disease (1-4). Currently the incidence of GBS-specific EOS has declined to 0.3-0.4 cases per 1000 live births, and overall EOS incidence has declined to 0.8-1.0 cases per 1000 live births (5-7). The microbiology of EOS has also shifted in the era of GBS prophylaxis. GBS remains the single most frequent cause of EOS among term infants, but *E. coli* is now the most frequent EOS pathogen in VLBW infants (4, 6, 8, 9). Morbidity and mortality remain substantial among infants who still suffer EOS, with virtually all VLBW and roughly half of term infants requiring neonatal intensive care for respiratory distress and/or blood pressure support (6). Despite this care, 2-3% of term and 20-30% of preterm infants still die of EOS (6, 10).

Corresponding author: Karen M. Puopolo, M.D., Ph.D., Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115. Phone: 617-525-7737 Fax: 617-278-6983, kpuopolo@partners.org.

Faced with a low-incidence, high-consequence disease, neonatal clinicians seek early identification of infants with EOS, with the goal of identifying those at risk and administering antibiotic treatment to prevent the progression to severe disease. Neonates who present with signs of critical illness from birth are universally treated with empiric antibiotics until sepsis is excluded by sterile cultures. Clinicians often choose to treat these infants with prolonged empiric therapy due to concern for culture-negative infection. Other newborns that ultimately develop symptomatic EOS may appear well, or only minimally and non-specifically ill, in the initial hours after birth. Among well-appearing infants, the clinician must identify those with colonization or early bacteremia that places them at risk for progression to symptomatic EOS. Both groups of infants present the clinician with a need to assess the risk of EOS to guide clinical care.

## Pathogenesis of EOS

The pathogenesis of EOS has long been recognized as infection originating during the intrapartum period, via the amniotic cavity to the fetus, originally termed the “amniotic infection syndrome.” In 1959 Benirschke (11) used placental histology and fetal and neonatal autopsies to demonstrate that the most common route of early-onset neonatal bacterial infection was that of ascending infection with maternal vaginal flora. He noted the bacteria cultures from the maternal vagina were usually identical to those found in infected neonatal lungs. He correlated the extent of inflammatory change within the placenta and umbilical cord with characteristics of labor, and with neonatal infection, demonstrating that both were associated with premature birth, length of labor and duration of rupture of membranes (ROM). Benirschke argued that with this understanding of the pathogenesis of EOS, the important question for clinicians was not whether antibiotic treatment of infected newborns would be effective, but “…whether antimicrobial therapy of the mother in suspected cases can definitely prevent prenatal infection or whether such therapy would begin to treat the infected babies before they are born.” Blanc in 1961 (12) addressed the issue of neonatal EOS risk assessment, writing, “The diagnosis of infection in the neonatal period presents considerable difficulties, and the prophylactic administration of antibiotics to infants carries dangers that should be weighed against the actual risk of infection. Objective criteria of intrauterine exposure to infection may be derived from our knowledge of the pathogenesis of prenatal infection and might help to screen the ‘high risk’ babies.” He suggested that “objective criteria” should include “severe maternal pyrexia,” prolonged labor, prolonged rupture of membranes, premature labor and persistent fetal tachycardia.

With the understanding the neonatal EOS originates in the antenatal/intrapartum period, multiple subsequent studies have assessed the role of specific maternal and neonatal characteristics in predicting risk of neonatal EOS, as well as the efficacy of intrapartum maternal antibiotic therapy and postnatal newborn antibiotic therapy. With the emergence of GBS as the single most common neonatal pathogen in the United States, many studies since the 1970's have focused on risk of GBS-specific EOS.

## Intrapartum risk factors for neonatal EOS

Information that is available during labor, prior to birth, can be used to assess risk and guide both intrapartum and neonatal management.

## Gestational age

The strongest predictor of EOS risk within the overall birth population is low gestational age (GA). Preterm infants are at significantly higher risk of EOS compared to term infants; the magnitude of the difference varies with gestational age but the disparity has remained significant even as the overall incidence of infection has declined for both term and preterm

infants. Active surveillance from 2005-08 reports overall EOS incidence of 0.77 cases/1000 live births, but this breaks down to ~0.5 cases/1000 among those born at ≥ 37 weeks, compared to ~3.0 cases/1000 live births occurring at < 37 weeks gestation (5). Much of the risk disparity among preterm infants is attributable to a 10-fold higher incidence among low-gestation, VLBW infants (~11 cases/1000 live VLBW births in 2006-2009 (13)) compared to the overall birth population, but even moderate prematurity is associated with increased risk. Infants born at 34-36 weeks gestation have 2-3 fold higher incidence of EOS compared to those born at 37-40 weeks (14, 15). Low GA and low birth weight (BW) are often used interchangeably, and are highly interactive, but the increased risk of neonatal EOS is more strongly associated with low GA than with BW (16). Extremely low gestation is associated with poorly-developed innate immune responses and deficiency of maternally-derived, passively-acquired, pathogen-specific antibody (17). When analyzed by gestational age within a VLBW cohort, a gradient of increasing risk is observed as gestation decreases from 28 to 22 weeks (13).

## Maternal intrapartum fever and chorioamnionitis

Although it was established as a risk factor for EOS on the basis of histologic examination of the placenta, in practice chorioamnionitis is diagnosed by clinical criteria, including intrapartum maternal fever; fetal tachycardia; uterine tenderness; foul odor of the amniotic fluid; maternal tachycardia or maternal leukocytosis (7, 18). Analysis and culture of amniotic fluid can also be used in clinical practice, with elevated WBC, low glucose levels, positive gram strains and bacterial growth diagnostic of chorioamnionitis (18). Chorioamnionitis is associated with 2-3 fold increased risk of EOS in live birth cohort studies of term infants as well as VLBW infants (adjusted for duration of ROM, GA and BW) (19, 20), and emerges as a significant predictor within Escobar, et al's study of at-risk infants born with BW > 2000 grams and evaluated for EOS (21). It is common clinical practice to use maternal intrapartum fever alone as a surrogate for chorioamnionitis. The risks of all-cause, GBS-specific and *E. coli*-specific neonatal EOS are associated with intrapartum fever, variably defined as peak maternal intrapartum temperature >37.5°C (99.5°F) or > 38°C C (100.4°F) (22-24). Risk increases with increasing height of maternal fever; in the EOS at-risk cohort study, 1.9% of evaluated infants were infected if maternal fever was < 99.5°F, but 6.4% of evaluated infants were infected when maternal fever was > 102°F (21).

## Duration of rupture of membranes

The fetal membranes form a barrier to ascending maternal genital tract bacteria. Invasive infection can rarely occur through intact membranes during prolonged labors (12) but most studies associate ROM as a significant risk factor for neonatal EOS. This risk factor can be further characterized by duration of ROM, in hours prior to delivery; premature ROM, occurring before onset of labor; or preterm ROM, defined as rupture before 37 weeks gestation (16), and assessment of ROM as an independent predictor of EOS risk is complicated by the fact that each of these definitions is associated with preterm delivery. In one of the earliest studies of risk factors for GBS-specific EOS, the obstetrical complication of ROM > 24 hours was observed in 62% of infants with GBS-specific EOS, in 11% of infants colonized (but not infected) with GBS, and in 5.8% of infants neither colonized nor infected with GBS (25). Notably, 80% of the infected infants in this study had BW < 2500 g. Boyer, et al (22) evaluated duration of ROM and demonstrated a steep increase in risk of GBS-specific EOS with ROM > 18 hours. This duration was associated with a 4-fold increase in the attack rate of GBS-specific EOS in a study in which 50% of cases occurred in infants with BW < 2500 grams. Studies adjusting for GA provide conflicting information in different categories of EOS. In a case-control study of risk factors for *E. coli*-specific EOS,

in which 2/3 of cases were born preterm, ROM > 18 hours is associated with 3-4-fold increases in risk of *E. coli*-specific EOS (24). In contrast, a case-control study matching for gestational age did not find ROM>18 hrs to be a significantly associated with GBS-specific or non-GBS-specific EOS unless intrapartum fever was also present (23). In Escobar's cohort study of at-risk infants (>80% of whom were born ≥ 37 weeks gestation), ROM > 12 hours was a significant predictor of all-cause EOS (21). Yet a cohort study of VLBW infants found only ROM > 48 hours predicted increased risk of EOS compared to that of the overall cohort (26). These findings likely reflect different pathogenic contributions of ROM: among very preterm infants, ROM may be a consequence of the ongoing infectious process that results in preterm delivery. In most cases, ROM provides opportunity for ascending colonization of placental and fetal tissues, and the consequences of that colonization are different depending on the colonizing organism and level of immune function available at different gestational ages.

## GBS colonization

Maternal GBS colonization is a prerequisite for neonatal GBS-specific EOS. Multiple studies demonstrate that women are variably colonized with GBS in their gastrointestinal and genitorurinary tracts; point-prevalence studies of pregnant women report colonization rates of 10-30% (7). A longitudinal study of 1248 non-pregnant, sexually-active women found that nearly 60% were colonized at least once when evaluated for a year at 4-month intervals (27). Because maternal GBS colonization is not universal, multivariate analyses of risk factors for GBS-specific EOS demonstrate that maternal GBS status is the overwhelming predictor of risk, with odds ratio >200 (16). The absence of protective, maternally-derived, polysaccharide capsular-specific antibody to GBS correlates with incidence of infection (28). Intrapartum administration of appropriate antibiotic therapy (IAP) can decrease infant colonization to <10% and decrease invasive disease by 90% (29-31). In the first randomized study of the efficacy of GBS IAP, the overall attack rate for GBS-specific EOS was 10.2/1000 in the absence of maternal IAP, or approximately 1% of infants born to GBS-colonized mothers (31). However, when maternal colonization status in this study is subcategorized by the presence or absence of additional characteristics, very different levels of risk become apparent (31). Among the infants born to GBS-colonized women with labors complicated by ROM > 12 hours and/or birth < 37 weeks gestation, the attach rate was 63/1000; among those born to women with labors complicated by maternal fever ≥37.5°C, the attack rate was 130/1000. But for those infants born to GBS-colonized women *without* additional intrapartum risk factors, the attack rate was 4.3/1000 - emphasizing the importance of multiple considerations in assessing the risk presented by maternal GBS colonization. In each of these categories, there were no cases of GBS-specific neonatal EOS occurred after the administration of IAP. With the widespread of implementation of GBS IAP, most GBS-specific EOS now occurs among premature infants or among term infants born to mothers who have screened GBS negative (32, 33).

## Maternal demographic factors

Maternal age < 20 years was identified in pre-GBS IAP era studies as risk factor for GBS-specific EOS but young age may also be a surrogate for factors associated with higher rate of GBS colonization (34) and in later studies, maternal age is not a significant risk factor for GBS-specific or non-GBS EOS (23). Maternal black race is persistently identified as risk factor for GBS-specific EOS (23, 33-35). Although African-American race is associated with higher incidence of GBS colonization among young, nonpregnant women (27), the persistently higher incidence of GBS-specific EOS among black infants is not explained by differences in rates of GBS colonization, GBS screening or administration of GBS IAP (33). Furthermore, recent multistate active surveillance reveals significantly higher incidence of

all-cause EOS among both preterm and term black infants (5). This racial disparity remains unexplained, possibly due to unmeasured aspects of health affected by socio-economic status or by differences in maternal opsonic antibody responses not captured in current studies.

## Other intrapartum risk factors

Obstetric practices that may promote ascending infection with vaginal flora, and/or disruption of amniotic membranes – increased frequency of intrapartum vaginal exams, invasive fetal monitoring, “membrane-stripping” to promote onset of labor, pharmacologic cervical ripening agents - have been variably associated with increased risk of EOS from observational studies (7, 23). The delivery of a previous infant with GBS-specific EOS is associated with increased risk in a subsequent delivery (36), a factor that may be related to an individual's inability to mount a protective antibody response to GBS, or to carriage of a particularly virulent GBS strain.

## Postnatal Risk Factors

In the postnatal period, EOS risk assessment must account for neonatal status as well as intrapartum characteristics. Both neonatal clinical status (characterized as symptomatic or symptomatic) and laboratory evaluation are used to determine the need for EOS evaluation and for empiric use of antibiotics. These factors primarily affect decision-making among term infants, as clinical instability and laboratory abnormalities are so frequently observed among VLBW infants in the absence of infection.

## Neonatal clinical status

Pre-GBS IAP era studies demonstrate a lower incidence of EOS among asymptomatic infants evaluated for EOS on the basis of intrapartum risk factors, as compared to infants evaluated for symptoms of illness. One study of infants born ≥ 37 weeks found bacteremia among 0.5% of evaluated, asymptomatic infants versus 3.2% of evaluated, symptomatic infants (37). Escobar et al (21) found an adjusted odds ratio for EOS of 0.26 (95% confidence interval, 0.11-0.63) among asymptomatic infants when compared to symptomatic infants evaluated for EOS. We found that bacteremia was diagnosed in only 0.28% of asymptomatic infants born at ≥ 35 weeks gestation at our institution, a large perinatal center with screening-based GBS IAP. (38). Asymptomatic status alone cannot rule out infection, however; in each of these cited reports, the incidence of EOS among the asymptomatic, evaluated infants was still 2-3 times than that of the entire birth cohort (21, 37, 38).

## Neonatal laboratory evaluation

The value of specific neonatal laboratory tests in the assessment of EOS risk depends on whether the test is used to predict culture-proven disease or clinical EOS, as well as whether it is used to assess risk among asymptomatic or symptomatic, term or preterm infants. In any case, no single test has sufficient sensitivity and specificity to be used in isolation, and thus these tests are best used as adjunctive data in specific clinical contexts.

## White Blood Count (WBC)

The WBC and differential is readily available and commonly used to evaluate both symptomatic and asymptomatic infants at risk for EOS. Interpretation of neonatal WBC has been compromised by the relatively small size of studies used to determine normal values, and by a lack of data quantifying the impact of differences mediated by gestational age,

postnatal age, mode of delivery and maternal and neonatal non-infectious clinical conditions. Until recently, the standard for interpreting early neonatal WBC values was derived from a 1979 study by Manroe and colleagues (39). This landmark study used less than 300 values obtained from 108 infants representing a mix of symptomatic and asymptomatic infants with a wide range of non-infection diagnoses to determine normal ranges for WBC, absolute neutrophil count (ANC) and the ratio of immature to total neutrophils (I:T). Subsequent studies using cut-off values of normal derived from this work have demonstrated poor sensitivity and specificity in predicting infection among at-risk term and late-preterm newborns when evaluated shortly after birth (21, 40) or with serial values over the first 24 hours of life (41). One important finding of the Manroe work is the “roller coaster” shape of the WBC, ANC and I/T curves in the first 72 hours of life, suggesting that optimal interpretation of WBC data to predict EOS should account for the natural rise and fall in WBC during this period. The development of electronic medical records has allowed larger analysis of this issue. One study of 30,354 WBC's from an integrated healthcare system stratified neutrophil values by time after birth and by gestational age and found a higher upper limit of ANC than the Manroe study, although neutropenia was defined similarly. Infants born after maternal labor versus no labor, and female infants compared to male infants, had higher average ANC. By excluding infants with blood-culture proven EOS, chromosomal abnormalities, or extreme WBC results, as well as infants born to mothers with pre-eclampsia, the study aimed to approximate a “normal” cohort to which at-risk infants could be compared (42). A 2010 study of WBC and culture-proven EOS suggests that the use of interval likelihood ratios may be superior to labeling individual values “normal or abnormal” based on cut-off values of normal (43). This study included 67,623 CBC and blood culture pairs obtained in the first 72 hours of life from infants born at ≥ 34 weeks gestation; it included 245 cases of blood-culture proven infection. Improving likelihood ratios were observed for the total WBC, ANC and I/T when these values are measured after 1-4 hours of life. Both the WBC and the ANC were most predictive of infection when these values were low (WBC <5,000; ANC <1,000) and elevated WBC (>20,000) was not useful. The I/T was the most informative metric if measured at < 4 hours of life; low values (< 0.15) were reassuring while elevated values (> 0.30) were associated with EOS, but the likelihood ratios are all relatively low. Adjusting for factors such as BW, maternal pre-eclampsia, gender and mode of delivery did not improve the overall predictive value of the WBC and its components. This study supports the use of WBC only after the first few hours of life among term and late-preterm infants, when placed in the proper clinical context.

## Acute-phase reactants and inflammatory mediators

C-reactive protein (CRP) is produced in the liver, and is a nonspecific marker of inflammation. Procalcitonin (PCT) is a peptide precursor of the hormone calcitonin which increases more rapidly in the course of infection. Both have been evaluated as predictors of EOS (44-48). CRP increases late in the course of infection, and a single determination of CRP at birth lacks both sensitivity and specificity for EOS. Serial CRP determinations have been used to estimate EOS risk and guide length of antibiotic treatment for symptomatic infants with culture-negative clinical sepsis (45, 48). In a recent meta-analysis of PCT, six included studies (with a total 780 neonates) evaluated its role in predicting risk of EOS. The six studies defined EOS as either culture-proven infection or evidence of clinical sepsis, included broad ranges of GA, had significant statistical heterogeneity, and most study infants were symptomatic. The pooled sensitivity and specificity of PCT in predicting EOS was 76%, with improving sensitivity after 24 hours of life (47). Finally, inflammatory molecules such as interleukin-6, interleukin-8, interleukin-10, interleukin-1 β, G-CSF, and TNF-alpha, as well as measurements of inflammatory cell-surface markers such as CD64 have been variably correlated with culture-proven, clinical and viral sepsis (48, 49). None of

these biomarkers are currently validated as screening tools for EOS risk assessment. Proteomic analysis may provide a means of finding specific markers with better clinical utility in EOS risk assessment (51).

## Clinical neonatal EOS risk assessment in the era of GBS prophylaxis

Armed with the information reviewed here, perinatal caregivers should have clinical policies to determine which newborns need evaluation for EOS, and whether the evaluation should include empiric antibiotic therapy. The CDC 2010 revised guidelines for prevention of perinatal GBS disease provide recommendations for neonatal evaluation to prevent both GBS-specific and all-cause EOS, which may be used as the basis for local policy. The recommendations include EOS evaluation for infants born to mothers who received inadequate GBS IAP if additional risk factors (ROM > 18 hours or preterm delivery) are present; and evaluation and empiric antibiotic therapy for EOS for infants of all gestational ages with symptoms of sepsis, as well as for asymptomatic infants born to mothers with chorioamnionitis. Recommended components of neonatal evaluation include at minimum CBC and blood culture, with lumbar puncture and chest radiograph reserved for symptomatic infants. Accounting for the evidence reviewed here, the CDC does not recommend evaluation of acute phase reactants and endorses the option of obtaining WBC and differential at 6-12 hours of life (7).

Other issues should be considered in the development of local neonatal risk assessment policy. The majority of the information on neonatal EOS risk assessment that informs the CDC recommendations is derived from studies performed prior to the widespread implementation of GBS IAP. Additional obstetric indications for maternal antepartum and/or intrapartum antibiotics include threatened preterm labor, preterm rupture of membranes, and concern for chorioamnionitis (7). It is anticipated that administration of GBS IAP and intrapartum antibiotics for GBS-negative women with intrapartum fever would lead to intrapartum antibiotic administration in ~30% of labors (7); in our large high-risk perinatal center, antibiotics are used in ~40% of vaginal deliveries (4). Neonatal EOS risk assessment should account for shifts in local obstetric antibiotic practices. The overall impact of EOS risk assessment on local patient care and resource utilization also bears consideration. Nearly all VLBW infants are evaluated for EOS, and most are treated with empiric antibiotic therapy (52, 53). Using policies based on risk factors for EOS including maternal GBS status, ROM >18 hours and maternal intrapartum fever, studies performed prior to the first 1996 CDC guideline report 15-21% of all term infants evaluated for EOS, one-half to two-thirds of which were asymptomatic at the time of evaluation, and 30-100% of which received empiric antibiotic therapy (21, 37). At our institution, using a local algorithm based on the 2002 CDC guidelines, 15% of asymptomatic infants are evaluated for EOS, and half of these infants received empiric antibiotic therapy (38). These findings are consistent with population estimates of risk factor prevalence that predict evaluation of 16-17% of infants born ≥ 34 weeks gestation (15). Although designed for neonatal safety, this level of evaluation and empiric therapy may also have negative financial, social and long-term health effects.

Multivariate analysis of neonatal EOS risk presents an opportunity to refine criteria for evaluation and therapy. Algorithms that rely on dichotomous cut-off values to define risk potentially waste information by failing to quantitate the difference in risk between extreme values, and ignoring the risk presented by values below the chosen threshold. In addition, as noted here, many of the risk factors for EOS are interactive – for example, prolonged ROM is associated with low gestational age. Given that baseline EOS incidence remains 10-fold higher among preterm infants in the era of GBS prophylaxis, clinical risk assessment is best done separately for term and preterm infants. Two recent studies have developed

multivariate models for more accurate assessment of EOS risk that account for gestational age and intrapartum antibiotic exposure.

Dutta, et al performed a prospective cohort study of 601 mother/infant pairs born ≤ 34 weeks gestation, within which 85 infants had culture-proven EOS (54). Intrapartum antibiotics were administered to 23% of the mothers. Univariate analyses were performed for multiple established risk factors for EOS. An accurate predictive model was developed using multivariate logistic regression (c statistic 0.75) with the predictors BW < 1500 grams, GA < 30 weeks, male sex, lack of intrapartum antibiotics, and clinical chorioamnionitis. The authors translated this into a risk score using weighted integer values for each predictor and demonstrate good correlation of total score with both risk of EOS and risk of neonatal death. The application of this model to general practice is limited by several factors; the study cohort was from India, where the incidence of neonatal GBS-specific EOS is very low; the incidence of culture-proven EOS within the cohort was exceedingly high (140/1000); and the prospective cohort study design was compromised by the fact that 18% of infants were from multiple gestation pregnancies. But this study suggests that multivariate approaches to EOS risk could be applied to a primarily VLBW population to limit empiric antibiotic therapy even in this relatively high-risk population.

We recently performed the largest case-control study of all-cause EOS among infants born at ≥ 34 weeks in the era of GBS prophylaxis (15). This study re-evaluated the relationship of specific intrapartum factors to neonatal EOS risk in the era of GBS prophylaxis and sought to determine how risk has been modified both by GBS-specific IAP and all forms of intrapartum antibiotic therapy. This information was used to develop a multivariate risk model for the term and late-preterm population. The study specifically focused on objective clinical information that could be derived from an electronic medical record, to provide the clinician with an estimation of EOS risk at the moment of delivery, independent of the clinical condition of the infant. Multiple risk factors were considered; the final model included GA, highest maternal intrapartum temperature and duration of ROM as continuous variables; and maternal GBS status and intrapartum antibiotic therapy as dichotomous variables, with the latter represented as type of antibiotic (GBS-specific or broad-spectrum) and duration of administration (greater than or less than 4 hours prior to delivery). Maternal age, race, and epidural analgesia were considered as predictors but did not provide additional value in the final model. The relationships of GA, maternal intrapartum temperature, and duration of ROM to EOS risk derived from this study demonstrate the advantage of continuous as opposed to dichotomous consideration of the risk factors. Decreased risk of EOS was observed as gestation advanced from 34 to 38-40 weeks, but risk increased again at 41-42 weeks. Maternal temperature was linearly related to small increases in EOS risk below 100.5°F (38.0°C), but above that level, risk rose rapidly with increasing temperature. In contrast, duration of ROM was continuously but monotonically related to increased EOS risk. The final multivariate model accounted for all of these different relationships, as well as for intrapartum antibiotic use. On bivariate analysis, the administration of intrapartum broad-spectrum antibiotics defined infants with increased risk of EOS. However, multivariate modeling demonstrated the protective effect of all forms of intrapartum antibiotic therapy, when other risk factors are considered, highlighting the difficulty of confounding by indication when assessing EOS risk.

The final multivariate model developed from this study had good discrimination (c statistic 0.800) and provides the clinician with a prior probability of EOS at the time of birth, based solely on objective intrapartum information. From a practical perspective, the clinician can combine this probability with neonatal clinical status, and later laboratory evaluation, to guide decisions of evaluation and empiric treatment. This approach does force the clinician to define an acceptable level of risk, but also allows clinicians to account for local practices

and resources. Using a prior probability equal to the overall incidence of EOS among infants born ≥ 34 weeks (~0.5/1000), the model can identify as many EOS cases as those flagged by dichotomous risk approaches by evaluating less than half as many infants. The model can also provide an estimation of relative risk between specific clinical scenarios that are not distinguished by dichotomous risk algorithms. This model is intended for use within an electronic medical record but a web-based version with manual input of required data is available at http://www.dor.kaiser.org/external/DORExternal/research/InfectionProbabilityCalculator.aspx.

## Unanticipated consequences of neonatal EOS risk assessment

The focus of EOS risk assessment is the early identification of maternal and neonatal issues for which intervention - primarily the empiric administration of intrapartum and/or neonatal antibiotics – should be taken for infant safety. The efficacy in intrapartum antibiotics to prevent neonatal EOS is now well-established. Concerns have been raised in regard to the neonatal safety of IAP with respect to potential emergence of antibiotic-resistant EOS, and delays in presentation of symptomatic EOS. Aside from the apparent increase in macrolide-resistant GBS, and ongoing debate regarding the incidence of ampicillin-resistant EOS among VLBW infants, these concerns have not been born out (4, 21, 32, 55, 56). Recently, the safety of empiric neonatal antibiotic treatment is being questioned. Studies performed among uninfected premature infants demonstrate that antibiotic therapy in the first week of life is associated with increased risk of fungal infection, bacterial late-onset sepsis, necrotizing enterocolitis and death (53, 57-59), even when controlled for gestational age, surrogates of severity of illness, and breast milk feeding. These particular concerns are not likely to be relevant to the health of asymptomatic term infants. However, a prospective, longitudinal birth cohort study performed in Sweden found that exposure to antibiotics in the first week of life was associated with increased risk of recurrent wheezing disorders by age 12 months, even when the analysis was restricted to infants born at ≥ 37 weeks (60). Risk persisted through 4.5 years of age (61). The biologic basis for these effects of early antibiotic exposure remains uncertain, but emerging data suggests that early antibiotic treatment may affect the development of the intestinal microbiome (62).

## Conclusions

Despite tremendous progress in neonatal EOS risk assessment and prevention, there remains a residual disease burden on infants of all gestational ages. Current intrapartum and neonatal prevention strategies result in significant levels of obstetric and neonatal antibiotic exposure, with largely undefined impacts on healthcare utilization, maternal/infant social development as well as on long-term health outcomes. Approaches to risk assessment and disease prevention are imperfect, although better data on the value of laboratory tests, development of multivariate risk measurement, and increased awareness of risk/benefit issues, particularly among VLBW infants, may offer opportunities for improvement. The development of sophisticated technologies for real-time measurement of biomarkers of infection; rapid and accurate methods of diagnosing bacteremia to replace traditional culture; better understanding of genetic variation that may contribute to individual risk for infection; and development of vaccine-based methods of EOS prevention, may all improve the clinician's approach to this low-incidence, very high-risk newborn illness.

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## Abbreviations

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| **ANC** | Absolute neutrophil count |
| **BW** | Birth weight |
| **CDC** | Centers for Disease Control and Prevention |
| **EOS** | Early-onset sepsis |
| **GA** | Gestational age |
| **GBS** | Group B Streptococcus |
| **I: T** | Ratio of immature to total neutrophils |
| **IAP** | Intrapartum antibiotic prophylaxis |
| **ROM** | Rupture of membranes |
| **VLBW** | Very-low birth weight |
| **WBC** | White blood count |