



# Antenatal Screening for Group B Streptococcus in the Setting of Preterm Premature Rupture of Membranes: Empiric versus Culture-based Prophylaxis

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## Abstract

**Objective** Imperfect culture sensitivity and increase of early onset neonatal sepsis (EONS) risk in preterm neonates raise concern that culture-based intrapartum antibiotic prophylaxis (IAP) may be insufficient after preterm premature rupture of membranes (PPROM). Our objective was to compare rates of EONS after empiric versus culture-based IAP in PPRM.

**Study Design** This retrospective cohort study included women with a singleton gestation and PPRM between 23 and 33 weeks. Outcomes after culture-based IAP were compared with empiric IAP. The primary outcome was EONS. Secondary outcomes included group B streptococcus (GBS) bacteremia, bacteremia, and neonatal GBS infection. Bivariable and multivariable logistic analyses were performed.

**Results** Of the 270 women who met inclusion criteria, 136 (50%) had culture-based IAP of whom 36 (26.5%) were GBS positive. There was no significant difference in bacteremia (2.2 vs. 4.5%,  $p = 0.30$ ), GBS infection (0.8 vs. 0.7%,  $p = 1.00$ ), or EONS (11.8 vs. 12.7%,  $p = 0.82$ ) in infants of women with culture-based IAP compared with empiric IAP. Multivariable analysis confirmed a lack of advantage to empiric versus culture-based IAP in EONS risk (adjusted odds ratio [aOR] = 0.82, 95% confidence interval [CI]: 0.44–1.93).

**Conclusion** In pregnancies complicated by PPRM, infants of women who received culture-based IAP had no significant difference in EONS or GBS infection compared with infants of women with empiric IAP.

## Keywords

- ▶ preterm premature rupture of membranes
- ▶ early onset neonatal sepsis
- ▶ group B streptococcus culture

Group B streptococcus (GBS) bacteria colonizes the genital tract in 10 to 30% of pregnant women.<sup>1,2</sup> GBS colonization during pregnancy is the primary risk factor for neonatal GBS infection with its accompanying risks of significant infant morbidity and mortality.<sup>3–5</sup> Over the last several decades, intrapartum intravenous administration of antibiotics to women at risk for transmitting GBS has greatly reduced

neonatal disease.<sup>3,6,7</sup> Current CDC guidelines recommend routine screening for GBS at 35 to 37 weeks of gestation and subsequent administration of intrapartum antibiotics if the GBS screen is positive (universal culture-based prophylaxis).

However, this approach is complicated in the setting of preterm premature rupture of membranes (PPROM) which causes up to 30% of preterm births.<sup>8</sup> Prolonged rupture of

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membranes (>12 hours) is associated with increased risk of transmission of GBS to the newborn.<sup>9</sup> Furthermore, preterm infants are at an increased risk of GBS infection, early-onset neonatal sepsis (EONS), and severe infection with complications, particularly at <34 weeks of gestational age (GA).<sup>5,10,11</sup>

Women with PPROM will not yet typically have undergone routine outpatient GBS screening. In this case, the recommendation is to screen for GBS at the time of diagnosis of PPROM, prior to receipt of any antibiotics. Upon the diagnosis of labor or at the time of induction, the GBS status—if available—guides whether or not to use intravenous intrapartum antibiotics for GBS (i.e., a culture-based intrapartum antibiotic prophylaxis [IAP] approach).<sup>12</sup> If culture results are not available, empiric IAP is provided.<sup>3,13,14</sup>

While screen-based IAP has been shown to be superior compared with the treatment based on risk factors, there are no adequate data regarding reliability of GBS screening in the setting of PPROM.<sup>15</sup> Notably, in cases of neonatal GBS infections, up to 60 to 80% of women had a negative GBS screen.<sup>16</sup> Thus, the limitations in sensitivity of GBS culture, particularly in the context of PPROM, may result in insufficient IAP for some women.<sup>7</sup> Given the concerns for possible underdetection of GBS colonization and the increased morbidity and mortality associated with GBS infection in preterm neonates, it is currently unclear what the infectious morbidity is to neonates born to GBS-screen negative mothers. Therefore, the objective of this study was to evaluate if empiric IAP (administered universally to women with PPROM) is associated with reduced risk of EONS and neonatal GBS infection compared with culture-based IAP in the setting of PPROM.

## Methods

### Study Design and Subjects

We conducted a retrospective cohort study of women who delivered at Northwestern Memorial's Prentice Women's Hospital, a tertiary care hospital in Chicago, IL, between January 2010 and October 2015. Women were included if they were at least 18 years of age, carrying a singleton gestation, and were diagnosed with PPROM between 23 and 33 weeks. A total of 33 weeks was chosen as it afforded an opportunity for GBS cultures to result if they were sent. Mothers with suspected fetal anomalies were excluded.

Routine clinical care of women presenting with PPROM during the study period, in accordance with the American College of Obstetricians and Gynecologists (ACOG) guidelines,<sup>14</sup> included clinical confirmation of the PPROM diagnosis and assessment of fetal well-being. If a GBS culture was obtained, it was done via rectal and vaginal swab prior to initiation of maternal antibiotics. The swab was incubated in LIM broth overnight and then subcultured to sheep blood agar plate. Colonies with  $\beta$ -hemolysis were identified with Vitek MS, an automated mass spectrometry microbial identification system. Antenatal betamethasone was administered and if labor had not ensued, latency antibiotics were initiated. These consisted of ampicillin and erythromycin for a total of 7 days. If PPROM was diagnosed prior to 32 weeks, women were started on magnesium for fetal neuroprotection and were monitored

on the Labor and Delivery Unit for at least 12 hours. Thereafter, if maternal and fetal stability remained, they were transferred to the inpatient antepartum unit for close monitoring. Delivery was recommended if there was concern for chorioamnionitis (maternal temperature  $\geq 100.4$  F along with clinical signs and symptoms of intra-amniotic infection) or a clinically significant abruption. If preterm labor developed, women were transferred back to Labor and Delivery for monitoring but tocolysis was not administered. In the absence of a contraindication to expectant management or preterm labor, an induction was planned for 34 weeks of gestation. One rescue course of antenatal steroids was reserved for cases with the documentation of a clinical change which was suggestive of anticipated delivery within 7 days. Notably, during the study period, the decision to utilize empiric IAP or culture-based IAP in the setting of PPROM was left to the discretion of the attending obstetrician. According to Center for Diseases Control and Prevention guidelines in the United States, penicillin or ampicillin was used for prophylaxis in women without penicillin allergy. Alternate antibiotics include cefazolin in women at low risk of anaphylaxis, clindamycin, and vancomycin.<sup>3</sup> All GBS cultures obtained and used for medical decision-making were obtained prior to initiation of any maternal antibiotics.

Comprehensive clinical data were abstracted from maternal and infant electronic medical records by authorized research personnel. Maternal data included sociodemographics, past medical history, past obstetrical history, labor, and delivery outcomes including length of antepartum admission, indication for delivery, development of fever or chorioamnionitis, and laboratory findings including GBS screening culture. Data on maternal antibiotic administration was abstracted, including GBS IAP and administration of latency antibiotics, for which standard of care was to administer ampicillin and erythromycin for 7 days. Neonatal data were obtained from linked chart within the electronic medical record system. Neonatal data included temperature abnormalities (recorded as the highest and the lowest temperature), clinical diagnosis of sepsis, any infectious workup results (e.g., CBC with differential, C-reactive protein [CRP], blood and cerebrospinal fluid cultures), and antibiotic and administration.

### Infant Outcomes

The primary endpoint was EONS. Based on culture results, antibiotic treatment and laboratory data, patients were classified as having EONS using predetermined criteria based upon National Institute of Child Health and Human Development definitions for premature infants.<sup>11</sup> EONS was defined as having received an antibiotic treatment course of  $\geq 5$  days starting within 72 hours of life and either (1) a positive bacterial blood culture  $\leq 72$  hours of life or (2) other abnormal laboratory results indicative of infection. Abnormal laboratory results indicative of infection were: CRP  $\geq 1$  mg/dL,<sup>17</sup> absolute neutrophil count outside normal range for GA,<sup>18,19</sup> or immature-to-total (I:T) neutrophil ratio  $> 0.22$ .<sup>20</sup> Analyses were done using one and two abnormal laboratory indices as criteria for presumed EONS. The secondary neonatal outcome measure was early onset neonatal GBS infection, defined as GBS bacteremia and/or meningitis. A subgroup analysis was conducted

among women who were not on latency antibiotics at the time of delivery.

### Statistical Analyses

Bivariate analysis of demographics, risk factors, and outcomes were conducted using Chi-squared or Fisher's exact tests for categorical variables and Student's *t*-test or Wilcoxon's rank sum tests for continuous variables. Multivariable analysis was performed to study the association between IAP strategy and EONS/GBS infection. *p*-values of <0.05 were considered statistically significant. STATA software, version 13.1 (College Station, TX) was used for this analysis.

### Ethics Statement

The study was approved by the Northwestern University Feinberg School of Medicine Institutional Review Board prior to its initiation. Investigations were conducted according to the principles expressed in the Declaration of Helsinki.

## Results

### Maternal Data

There were 270 maternal/infant pairs that met inclusion criteria. Culture-based IAP was performed in 136 (50.4%) women and the remaining 134 women were given empiric IAP. Of women with culture-based IAP strategy, 36 (26.5%) were GBS positive and received antibiotics during labor and delivery. The remaining 100 did not receive IAP toward GBS prophylaxis. ► **Table 1** shows maternal characteristics. There

**Table 1** Maternal Characteristics stratified by intrapartum antibiotic prophylaxis strategy

	Empiric IAP	Culture-based IAP	<i>p</i> -Value
	<i>n</i> = 13	<i>n</i> = 136	
Advanced maternal age	25 (18.7)	25 (18.4)	0.95
Race/ethnicity			0.85
Non-Hispanic white	46 (34.9)	48 (35.6)	
Non-Hispanic black	35 (26.5)	30 (22.2)	
Hispanic	20 (15.2)	22 (16.3)	
Asian	6 (4.5)	11 (8.2)	
Other/unknown	25 (18.7)	24 (17.8)	
Nulliparous	76 (56.7)	80 (58.8)	0.73
Prior preterm birth	28 (20.9)	24 (17.7)	0.50
BMI at delivery (kg/m <sup>2</sup> )	29.0 (25.1–32.6)	28.5 (25.2–32.9)	0.92
Tobacco use	4 (3.0)	8 (5.9)	0.25
Diabetes (pregestational or gestational)	9 (6.7)	13 (9.6)	0.38

Abbreviations: BMI, body mass index; IAP, intrapartum antibiotic prophylaxis. Note: data presented as *n* (%) or median (interquartile range).

**Table 2** Antenatal and delivery data stratified by intrapartum antibiotic prophylaxis strategy

	Empiric IAP	Culture-based IAP	<i>p</i> -Value
	<i>n</i> = 134	<i>n</i> = 136	
Antenatal steroids	111 (82.8)	117 (86.0)	0.47
Induction of labor	22 (16.4)	27 (19.9)	0.46
Preterm labor	85 (63.4)	87 (64.0)	0.93
Cesarean delivery	38 (28.4)	42 (30.9)	0.65
Chorioamnionitis	18 (13.4)	21 (15.4)	0.64
Gestational age at delivery (wk)	32.0 (29.9–33.1)	31.9 (29.3–33.5)	0.82
Infant sex (M)	67 (50.0)	65 (47.8)	0.72
Birth weight	1,773 ± 515	1,695 ± 541	0.23

Abbreviation: IAP, intrapartum antibiotic prophylaxis.

Note: Data presented as *n* (%), median (interquartile range), or mean ± standard deviation.

were no differences in advanced maternal age, race/ethnicity, parity, history of a prior preterm birth, body mass index at delivery, tobacco use, or diabetes between women who received culture-based IAP versus empiric IAP.

Details of the antenatal management and delivery were also largely similar between groups including receipt of a complete course of antenatal steroids, preterm labor, route of delivery, induction of labor, need for emergent delivery, and chorioamnionitis (► **Table 2**). As anticipated, the duration of latency was longer in the culture-based IAP compared with the empiric IAP (7.6 vs. 2.1, *p* < 0.001). About 64% of women in the cohort were on latency antibiotics at the time of delivery and 87% of women in the cohort received antibiotics within 7 days of delivery; 72% in empiric IAP versus 57% in culture-based IAP group (*p* = 0.01). Infant sex, gestational age at delivery, and birth weight were similar between groups.

### Infant Outcomes

Nine (3.3%) infants in the cohort had bacteremia in the first 72 hours of life that was treated with an antibiotic course. The organisms isolated in blood culture from infants of mothers in the empiric IAP group (*n* = 6) were *Escherichia coli* (*n* = 3), GBS (*n* = 1), *Klebsiella pneumoniae* (*n* = 1), and coagulase negative staphylococcus species (*n* = 1). Bacteremia in the culture-based IAP group infants (*n* = 3) were *E. coli* (*n* = 1), GBS (*n* = 1), and *Haemophilus influenzae* (*n* = 1). There was no difference in the risk of early-onset GBS infection, and the risk of bacteremia between groups (6/134 vs. 3/136) was not statistically significant (adjusted odds ratio [aOR] = 0.45, 95% confidence interval [CI]: 0.11–1.87; ► **Table 3**). Abnormal individual laboratory results indicative of infection (e.g., absolute neutrophil count, I:T ratio, and CRP) were also not significantly different between groups. We analyzed two grades of strictness of presumed EONS criteria by antibiotics and laboratory criteria. There was no increased risk of EONS by bacteremia and/or either one or two accessory laboratory criteria. While there were no differences identified in

**Table 3** Neonatal outcomes following empiric versus culture-based maternal intrapartum antibiotic prophylaxis

	Empiric IAP <i>n</i> = 134 (%)	Culture-based IAP <i>n</i> = 136 (%)	<i>p</i> -Value	aOR <sup>a</sup>	95% CI
Neonatal bacteremia	6 (4.5)	3 (2.2)	0.30	0.45	0.11–1.87
GBS bacteremia	1 (0.7)	1 (0.8)	1	N/A	N/A
Antibiotics ≥ 5 d	56 (41.8)	52 (38.2)	0.55	0.85	0.52–1.39
Absolute neutropenia	36 (26.9)	33 (24.3)	0.62	0.88	0.51–1.51
Elevated I:T ratio	33 (24.6)	32 (23.5)	0.83	0.91	0.51–1.62
Abnormal C-reactive protein	20 (29.9)	19 (26.4)	0.65	0.86	0.41–1.81
EONS (culture and/or 2 abnormal laboratories)	17 (12.7)	16 (11.8)	0.82	0.92	0.44–1.93
EONS (culture and/or 1 abnormal laboratory)	72 (53.7)	61 (44.9)	0.15	0.69	0.42–1.12

Abbreviation: aOR, adjusted odds ratio; CI, confidence interval; EONS, early onset neonatal sepsis; GBS, group B streptococcus; IAP, intrapartum antibiotic prophylaxis; I:T, immature-to-total ratio; N/A, not available.

<sup>a</sup>Adjusted for indication for delivery and gestational age at delivery.

bivariable analyses to inform potential confounders—given the strong empiric associates between the indication for delivery (i.e., preterm labor/chorioamnionitis vs. induction at 34 weeks) and gestational age at delivery and EONS—these variables were included as potential confounders in a multivariable regression. Our findings persisted after controlling for potential confounders (►Table 3). A subgroup analysis, examining only women who were not still on latency antibiotics at the time of delivery, (*n* = 96) demonstrated no significant differences in EONS (defined by culture and/or one abnormal laboratory result) by IAP management strategy (47.4 vs. 46.6%, *p* = 0.94). Of note, the two cases of infant GBS infection were born to mothers on latency antibiotics at the time of delivery, one in each IAP group.

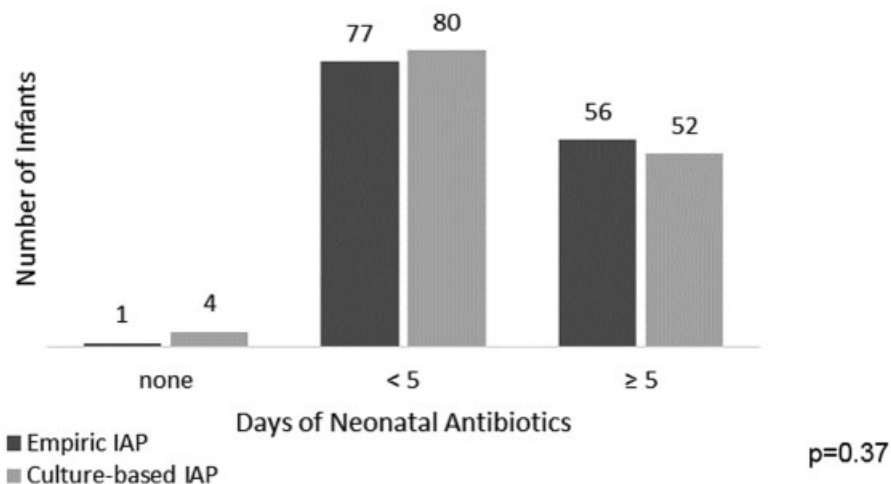
About 98% of infants had some systemic antibiotic exposure with 108 (40%) having received an antibiotic course ≥5 days. Early life antibiotic treatment of infants did not differ between groups, specifically infants receiving no antibiotics, <5 days of antibiotics (a “rule-out” of EONS), and ≥5 days of antibiotics (an antibiotic treatment course for proven or presumed EONS), as shown in ►Fig. 1. A post hoc

power calculation demonstrated that this study had 90% power to detect at least a two-fold difference in EONS between the two IAP strategies.

## Discussion

This study compares EONS and early-onset GBS infection in infants of mothers with PPROM prior to 33 weeks who received culture-based IAP versus those who received empiric IAP (without GBS screening culture sent). In our retrospective analysis, we found no significant difference in EONS or GBS infection between these IAP strategies. This study provides evidence supporting the current recommended guidelines for culture-targeted prophylaxis, even for women with PPROM and resultant preterm delivery.

The appropriate use of antibiotics in women with PPROM and high likelihood of preterm delivery is important for both maternal and infant outcomes. There are risks and benefits to widespread empiric antibiotic use, certainly administered directly to the infant, but also to mother prior to delivery. Risks include an increased risk of necrotizing enterocolitis in the



**Fig. 1** Days of early life neonatal antibiotic administration. Number of infant antibiotic days, with course starting in first 72 hours of life (early life antibiotics).

infant with early prolonged broad-spectrum antibiotics,<sup>21,22</sup> and recent ongoing research suggests that maternal antibiotics prior to delivery are associated with notable alternations in an infant's early life microbiome diversity. These microbial community changes have potential far-reaching effects on an infant's metabolic, immune, and allergic health.<sup>23</sup> Administration of certain antibiotics, however, have been shown to prolong gestational latency, important in reducing morbidities of extreme prematurity.<sup>14,24,25</sup> There has also been a significant decrease in GBS disease since institution of GBS IAP recommendations. Thus, antibiotic treatment in appropriate circumstances improves neonatal outcomes.

To date, there has been a paucity of data on the optimal strategy for IAP administration for women with PPRM, who do not have GBS culture results available at the time of rupture. The theoretical possibility of an increased risk of neonatal infection compounded by the imperfect sensitivity of culture particularly in the setting of PPRM led to this retrospective study. The negative predictive value of GBS culture declines outside a 5-week window between culture and delivery; thus, early screening would not address this problem. Our study reinforces that screening culture and culture result-based IAP decisions are not causing a missed opportunity for EONS prevention. Although our study was retrospective and culture proven, EONS is relatively infrequent; the point estimates of the incidence of bacteremia cases were lower in the culture-based IAP compared with empiric IAP cases. This finding provides reassurance that culture-based IAP is unlikely to result in an increased risk of EONS. Although our demographics demonstrate no difference in preterm versus induction of labor, it is possible that there was a shorter latency period and more rapid spontaneous preterm labor in the empiric IAP group—perhaps a reflection of underlying pathology related to increase risk of bacteremia. Recognizing the imperfect sensitivity of blood culture for EONS, we included presumed EONS based on laboratory criteria in our analyses and found no difference between IAP strategies. Furthermore, GBS infection was not different between groups which are the primary objective of the CDC's IAP guidelines.

The majority of women in both groups received antibiotics to promote gestational latency which remains standard clinical practice. There were significantly more women in the empiric IAP group who received latency antibiotics in the week preceding delivery. How latency antibiotics >7 days from delivery versus active treatment with latency antibiotics in the peripartum period effects EONS and neonatal GBS infection is unknown. Latency antibiotics could play a confounding or interaction role in the association between IAP and EONS, and thus requires further study.

The strengths of this study include detailed maternal and infant data on demographics, risk factors, antibiotics, and infant outcomes for a cohort of maternal-infant dyads. The granular definitions of EONS, incorporating both proven and presumed sepsis, microbiology results, and clinical antibiotic treatment decision strengthen the analysis of neonatal outcomes. A notable limitation in this study is the few infants with proven early-onset GBS infection and culture-proven

infection in general, which limits our power to detect potentially clinically important differences in this relatively rare but highly morbid condition.

In conclusion, this study demonstrates that a screen and culture-based IAP strategy for women presenting with PPRM at <33 weeks appears to be appropriate, without obvious missed opportunities for neonatal infection prevention and equivalent overall outcomes. Further data on timing of culture-based screening and other antibiotic treatments for PPRM management in larger prospective observational studies are necessary to advance perinatal care and optimize targeted antibiotic exposures to mother and infant.

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#### Conflict of Interest

None declared.

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