

## Research Article

### Diagnostic Quandary in Early-Onset Sepsis in Newborns and Implications for Management

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#### Abstract

##### Objective

To determine the incidence of and risk factors for Early-Onset Sepsis (EOS) in term and late-preterm neonates.

##### Study design

A retrospective chart review of term and late-preterm neonates evaluated for EOS and receiving empiric antibiotics. They were divided into positive (n=14) and negative (n=752) blood culture groups. Data were analyzed using Wilcoxon rank-sum and Fisher's exact tests.

##### Results

EOS incidence was 1.14/1000 live births. Non-respiratory symptoms (p=0.018) and positive chest x-ray (p<0.001) were more common in the positive blood culture group. Maternal risk factors, including group B streptococcus status, chorioamnionitis and prolonged rupture of membranes, were not significantly different between groups. Intrapartum antibiotic prophylaxis was more frequent in the negative blood culture group (p<0.001).

##### Conclusion

This study confirmed the inability of current risk assessment strategies to accurately identify EOS risk factors. Searching for better predictors is warranted to facilitate decreased antibiotic use in neonates at low risk for EOS.

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**Keywords:** Chorioamnionitis; Early-onset neonatal sepsis; GBS; Intrapartum antibiotics prophylaxis

#### Introduction

Evaluation of term and near-term neonates for Early-Onset Sepsis (EOS) remains problematic. EOS is an infrequent, but potentially devastating, condition. It is defined by the Centers for Disease Control and Prevention (CDC) as blood and/or Cerebrospinal Fluid (CSF) culture-proven infection occurring in a newborn less than 7 days of age [1]. A positive blood culture confirms sepsis and when the blood culture is negative, the condition is known as clinical sepsis [2].

The incidence of EOS in the United States (US) was reported as 0.98 per 1000 live births (range, 0.33-2.44 across centers) by Stoll et al in a study of more than 390000 live births between 2006 and 2009 at 16 university-based neonatal centers constituting the Neonatal Research Network [3]. Despite widespread implementation of Intrapartum Antibiotic Prophylaxis (IAP), early-onset Group B Streptococcus (GBS) disease remains the leading cause of EOS in term newborns [1].

Diagnosing sepsis has been a challenge for neonatologists, as its signs and symptoms are often nonspecific, the disease can quickly evolve to a more severe stage and no ideal marker of sepsis has been identified to date. The objectives of this study were to determine the incidence of EOS in term and late-preterm newborns in our institution and to determine the significance of clinical, laboratory and maternal factors in assessing the risk of EOS.

#### Materials and Methods

##### Experimental design

This is a retrospective electronic chart review study conducted at Kings County Hospital, an inner-city hospital in Brooklyn, NY, with a Level 3B Neonatal Intensive Care Unit (NICU). The State University of New York (SUNY) Downstate Medical Center Institutional Review Board approved the study and waived the need for parental consent.

All term and late-preterm (>34 weeks Gestational Age [GA]) babies born between January 2010 and December 2014 in Kings County Hospital Center who were evaluated for EOS and treated with empiric antibiotic therapy were included in the study. Babies born with major congenital malformations and preterm babies <34 weeks GA were excluded. Relevant demographic, clinical and laboratory data were collected from the electronic medical records.

Blood cultures were performed with an automated BACTEC system (BD Diagnostics, Franklin Lakes, NJ). Patients were assigned to

the positive blood culture group if at least one culture grew a known pathogenic species and antibiotic treatment was administered for at least 7 days. Cultures growing common skin flora (e.g. *Bacillus* species, coagulase-negative staphylococci) were considered contaminants if the infant remained well according to the primary care team, in the absence of appropriate antibiotic treatment. These infants were included in the negative blood culture group. The ratio of Immature to Total neutrophils (I/T ratio) was considered abnormal if it was >0.2.

## Statistical Analysis

Mean and standard deviation of birth weight and GA at delivery were compared between positive and negative blood culture groups using Wilcoxon rank-sum test. Fisher's exact test was used to compare groups for 10 potential risk factors. Bootstrap adjustment ( $2 \times 10^4$  replications) of p-values was applied to account for the multiple tests performed.

## Results

Among the 12,268 deliveries during the 5-year study period, 3,659 (29.8%) newborns were admitted to the NICU. Of these, 766 (21% of NICU admissions) were evaluated for EOS and received empiric antibiotic therapy. Nineteen newborns had positive blood cultures; in 5, the positive blood cultures were considered contaminants by the primary medical team and a full course of antibiotic treatment was not received. Therefore, 14 neonates (1.8% of the 766 evaluated newborns) were considered true positives, producing an EOS incidence of 1.14 per 1000 live births.

GBS was the most common organism associated with EOS, occurring in 7(50%) of the 14 newborns. Two babies had *Escherichia coli* and 2 had *Streptococci viridans*; the remaining organisms were *Staphylococcus epidermidis*, *Staphylococcus haemolyticus* and *Micrococcus*. None of the CSF cultures were positive. Demographic characteristics and the reasons for EOS evaluation (potential risk factors for EOS) are shown in table 1. There were no significant differences in GA, birth weight, mode of delivery, or sex between newborns with positive and negative blood cultures. Although the percentage of newborns with respiratory symptoms was not significantly different between negative and positive blood culture groups ( $p=1.00$ ), a positive chest x-ray and symptoms other than respiratory were significantly more common in the positive blood culture group ( $p<0.001$  and  $p=0.018$ , respectively). The percentage of neonates with an abnormal I/T ratio was not significantly different between groups ( $p=0.967$ ). Maternal risk factors, including a positive GBS screen, chorioamnionitis and prolonged rupture of membranes for >18h were also similar between groups ( $p=0.783$ ,  $p=1.00$  and  $p=0.820$ , respectively).

Use of IAP was significantly more common in the negative blood culture group ( $p<0.001$ ). Maternal fever, diagnosed as chorioamnionitis, was the most common factor leading to the neonates being evaluated for EOS in both cohorts (35.7% and 39.2% of neonates in the positive and negative blood culture groups, respectively).

In 5(35.7%) of the 14 newborns with positive blood cultures, the mother had a fever diagnosed as chorioamnionitis; none of these mothers received antibiotics before birth because the fever occurred intrapartum or postpartum. All except 1 of these infants had respiratory symptoms, other symptoms, or both (Table 2).

Variables	Positive blood culture group (n=14)	Negative blood culture group (n=752)	P value
Male sex	6/14(42.8%)	408/752(54.2%)	0.990
Gestational age (weeks), mean±SD	38.9±1.8	38.4±2	0.618
Birth weight (g), mean±SD	332±557	3191±630	0.442
Cesarean section	6/14(42.8%)	315/752(41.8%)	1.000
Chorioamnionitis	5/14(35.7%)	295/751(39.2%)	1.000
Maternal GBS colonization	1/12(8.3%)	188/655(28.7%)	0.782
PROM>18 hours	2/12(16.6%)	270/752(35.9%)	0.819
Intrapartum antibiotic prophylaxis	1/14(7.1%)	459/748(61.3%)	<0.001
Respiratory symptoms	10/14(71.4%)	546/752(72.6%)	1.000
Other symptoms	5/14(35.7%)	58/752(7.71%)	0.018
Abnormal I/T ratio	6/14(42.8%)	220/736(29.8%)	0.966
Positive chest x-ray	7/9(77.7%)	74/540(13.7%)	<0.001

**Table 1:** Demographic, clinical, laboratory and maternal characteristics of the positive and negative blood culture groups.

**Abbreviations:** GBS: Group B Streptococcus; I/T: Immature to Total neutrophils; PROM: Premature Rupture of Membranes; SD: Standard Deviation.

In 295 of the newborns with negative blood cultures, the mother had chorioamnionitis; in 67(22.7%) of these mothers, no antibiotics were administered before birth.

The incidence of GBS sepsis was 0.57 per 1000 live births. Of the 766 mothers evaluated in this study, 677 (87%) were screened for GBS (at a mean GA of 36 weeks) and 189 (28%) were found to be positive for GBS colonization. Of these, 154 (81%) received adequate prophylaxis. None of the babies born to mothers with documented GBS colonization developed GBS infection. All mothers of GBS-positive newborns were negative for GBS colonization except 1, in whom the GBS status was unknown (Table 3). None of these mothers received IAP. Two mothers of GBS-positive babies had prolonged rupture of membranes for >18 hours and 2 mothers had a fever (1 intrapartum and 1 postpartum).

For diagnosing EOS, the Negative Predictive Value (NPV) of a lack of neonatal symptoms (respiratory or other) was 99.4%. An abnormal I/T ratio had a NPV of 98.4% (516/524) and positive predictive value of 2.6% (6/226). The sensitivity and specificity of an abnormal I/T ratio were 42.8% (6/14) and 70.1% (516/736), respectively.

## Discussion

In this study, the incidence of EOS was 1.14 per 1000 live births, with GBS being the most common organism. Comparative analysis between negative and positive blood culture group revealed no significant differences in maternal risk factors, laboratory indicators, or clinical symptomatology, except the presence of non-respiratory symptoms and a positive chest x-ray in the neonate. Maternal fever (with presumed chorioamnionitis) was the most common reason for evaluating neonates for EOS in both cohorts. All babies with a positive blood culture had respiratory symptoms, other symptoms, or both, except for 1 neonate who was asymptomatic. Our study confirmed the inability of current risk assessment strategies to accurately identify predictors of EOS. Given the low rate of EOS, a search for better predictors is warranted to facilitate decreased use of antibiotics in term and late-preterm neonates at low risk for EOS.

Patient	Organism	Chorio	GBS Status	PROM >18 h	IAP	Resp Symp-toms	Other Symp-toms	Chest X-ray	Abnormal I/T Ratio
1	<i>Escherichia coli</i>	+	-	-	-	+	+	+	+
2	<i>Escherichia coli</i>	-	+	-	+	+	+	+	+
3	GBS	+	-	-	-	+	-	-	+
4	GBS	-	-	-	-	+	-	-	+
5	GBS	-	-	+	-	+	-	-	+
6	GBS	-	-	+	-	-	+	-	-
7	GBS	-	-	-	-	+	-	+	-
8	GBS	+	-	-	-	-	-	-	-
9	GBS	-	-	-	-	+	-	+	-

Table 2: Potential risk factors of neonates with positive blood cultures.

Patient	GA	Wt (g)	Sex (F/M)	C/S (Y/N)	Apgar at 1/5 min	Mat GBS	PROM>18 h (Y/N)	Mat Fever (Y/N)	Chorio (Y/N)	IAP (Y/N)	Resp Symp-toms (Y/N)	Other Symp-toms (Y/N)	I/T Ratio	Chest X-ray
1	37	2575	F	N	9/9	Neg	N	Y	Y	N	0	0	0.09	ND
2	41	3800	M	Y	3/7	Un	N	N	N	N	1	0	0.12	Pos
3	40	3515	M	N	9/9	Neg	N	N	N	N	1	0	0.19	ND
4	37	3290	F	N	9/9	Neg	Y	N	N	N	0	1	0.09	ND
5	39	3015	F	N	5/6	Neg	Y	Y	N	N	1	0	0.15	Pos
6	39	2970	F	N	9/9	Neg	N	N	N	N	1	0	0.26	Neg
7	41	3740	F	N	9/9	Neg	N	N	N	N	0	0	0.25	Neg

Table 3: Newborn, clinical, laboratory and maternal characteristics of neonates with group B streptococcus early-onset sepsis.

**Abbreviations:** Chorio: Chorioamnionitis; C/S: Cesarean Section; F: Female; GA: Gestational Age; GBS: Group B Streptococcus; IAP: Intrapartum Antibiotic Prophylaxis; I/T: Immature to Total neutrophils; M: Male; Mat: Maternal; ND: Not Done; Neg: Negative; Pos: Positive; PROM: Premature Rupture of Membranes; Resp: Respiratory; Un: Unknown; Wt: Birth Weight.

Our incidence of sepsis was higher than the reported overall incidence in the US. This may be at least partly because our population is predominantly African American. CDC surveillance data published in 2010 demonstrated a fourfold increased incidence of neonatal EOS due to GBS among African American infants when compared with white infants [4]. None of the mothers of our neonates with GBS EOS were positive for GBS on prenatal screening, consistent with the findings that most GBS in the US now occurs in mothers who have screened negative [5]. In a study by Edwards et al modern-day large cohort of all births over a 12-year period demonstrates a GBS colonization rate of 21.6% [6]. The estimated maternal GBS prevalence is 17.9% worldwide, ranging from 11.1% in Southeast Asia to 22.4% in Africa [7].

Bacterial culture remains the CDC-recommended standard for detecting maternal GBS colonization. In 2002, the US Food and Drug Administration approved the first Polymerase Chain Reaction (PCR)-based rapid diagnostic test for the detection of maternal GBS colonization [8]. The test can be completed in 1 hour and potentially allows for screening of pregnant women on presentation for delivery. Although this type of testing could address the risk of antenatal false-negative GBS screens and late colonization, the costs and technicalities of providing continuous support for a real-time PCR-based diagnostic test are considerable, so it is not widely used.

All except 1 of our neonates with a positive GBS-blood culture were symptomatic. This patient was born to a mother who did not receive IAP, as she developed fever postpartum. According to the multicenter prospective surveillance study by Wortham et al., signs

or symptoms of EOS were documented within 6 hours of birth in 200 (87%) of 229 chorioamnionitis-exposed infants [9]. Eight of the remaining 29 (28%) developed clinical evidence of sepsis within 72 hours after birth. All infants who died were symptomatic within 6 hours of birth.

Evaluation of EOS has evolved substantially over time. A revised algorithm based on the CDC 2010 GBS perinatal prevention guidelines eliminated 25% of all EOS evaluations and resulted in significant cost savings, without short-term evidence of harm [4]. These guidelines also recommended that well-appearing infants born to mothers with chorioamnionitis receive a limited diagnostic evaluation (Complete Blood Count [CBC] with differential and blood culture at birth) and empiric antibiotic therapy [10-13]. However, because the evidence behind these recommendations was limited to observational studies performed before the widespread use of IAP, whether diagnostic evaluations and empiric antibiotics are warranted for well-appearing term newborns exposed to chorioamnionitis is controversial [14]. Taylor et al., calculated the risk of EOS in a hypothetical infant with a normal physical examination at birth, who is born at term to a mother with chorioamnionitis; the risk is likely substantially <1% if the mother had a negative GBS screen [15]. In January 2015, the Eunice Kennedy Shriver National Institute of Child Health and Human Development invited an expert panel to a workshop to provide evidence-based guidelines for the diagnosis and management of pregnant women with chorioamnionitis and the neonates born to these women. The panel proposed to replace the term chorioamnionitis with “intrauterine inflammation or infection or both” and recommended guidelines for evaluation and management of pregnant women and

their newborns with this diagnosis [16]. A joint committee of Fetus and Newborn and committee on Infectious Diseases from American Academy of Pediatrics has published new guidelines which will help the clinicians to make reasonable and appropriate decisions regarding management of newborns with suspected or proven early onset bacterial sepsis [17].

In this study, most mothers (13/14; 92.8%) who gave birth to newborns with EOS did not receive IAP, although 5 had chorioamnionitis. The 1 neonate whose mother received IAP had respiratory and other symptoms on the first day of life. These findings suggest that all mothers with the diagnosis of chorioamnionitis should receive antibiotics and neonates born to mothers who received prophylactic antibiotics should be observed closely for signs and symptoms of infection. Neonates born to mothers who develop fever either intrapartum or postpartum should be monitored closely as well.

Our study has limitations. Because of its retrospective chart review design, the exact timing of symptom onset could not be clearly determined. Furthermore, the time at which the CBC tests were performed was variable.

In conclusion, current risk assessment strategies fail to accurately predict EOS and they unnecessarily expose many infants to antibiotics. Our study emphasizes the importance of close observation for signs and symptoms of infection as a more reliable diagnostic tool than current testing strategies and reemphasizes the importance of IAP.

## Conflicts of Interest

We declare that there are no competing financial interests in relation to the work described. The authors have no potential conflicts of interest to disclose.

## Presentations

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