

Predicting outcomes of neonates born to GBS-positive women who received inadequate intrapartum antimicrobial prophylaxis

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We determined the predicting factors of early-onset group B streptococcal (EOGBS) infection in neonates who were born to GBS carrier mothers with inadequate intrapartum antibiotic prophylaxis (IAP). Medical records of all neonates born from January 1, 2008 to April 1, 2010 were reviewed. Inadequate IAP was defined as delivery less than 4 hours (h) after the first administration of antimicrobial. Of 1910 neonates, 273 were born from mothers colonized with GBS, including 69 who received inadequate IAP. Of 69 neonates, nine showed symptoms, including respiratory distress, fever, tachycardia, vomiting, and irritability. Abnormalities in complete blood count (CBC) and C-reactive protein (CRP) were noted in three and four neonates, respectively. Three infants were diagnosed with EOGBS infection confirmed by positive rectal and throat cultures, and all three presented with respiratory distress and CRP abnormalities. Respiratory distress ($p=0.0004$) and CRP ($p=0.0001$) offered reliable indicators for detecting EOGBS infections.

Key words: group B streptococcus, C-reactive protein, blood cell count, premature rupture of membranes, chorioamnionitis.

Early-onset group B streptococcal (EOGBS) infection in newborns represents a major threat to neonates. In 2002, the Centers for Disease Control (CDC) guidelines regarding prevention of perinatal GBS infection first recommended maternal culture-based screening and intrapartum antibiotic prophylaxis (IAP) for women with positive screening results¹. The incidence of EOGBS infection has since declined dramatically from 1.7 cases per 1,000 live births in the early 1990s to 0.34-0.37 cases per 1,000 live births in recent years². The latest guideline published by the CDC in 2010 includes an algorithm for secondary prevention of EOGBS infection among newborns². The triage criteria illustrated in the guideline include clinical signs, maternal chorioamnionitis, gestational age, duration of premature rupture of the membranes, and implementation of IAP.

While IAP has been recommended to be implemented more than 4 hours (h) prior to delivery according to these guidelines, no well-designed studies have examined the safe duration of IAP to prevent EOGBS infections³. Both the current² and former guidelines^{1, 4} contain an optional recommendation to obtain a complete blood count (CBC) and blood culture from neonates whose mothers are GBS-carriers and received antibiotics starting less than 4 h before delivery. However, several studies have demonstrated that none of the blood cultures obtained from newborns who had received inadequate IAP were GBS-positive⁵⁻⁷. Moreover, the yield of CBC in the diagnosis of EOGBS infection remains unclear, particularly when obtained in the first 4 h post-delivery⁸.

The aim of this study was to determine the clinical characteristics of newborns whose

mothers received inadequate IAP before delivery. We were particularly interested in the clinical signs and laboratory characteristics of neonates born from GBS-positive mothers who started receiving antimicrobials less than 4 h before delivery.

Material and Methods

This study was conducted at Yokohama Municipal Citizens Hospital, Yokohama, Japan. It is a community hospital located in the middle of Yokohama, which is the second largest city in Japan by population after Tokyo. The mean annual birth rate within the institution is approximately 1,000.

We performed a retrospective cohort analysis of all GBS-carrier mothers and their infants from January 1, 2008 to April 1, 2010. Neonates with gestational age <35 weeks or major congenital anomalies were excluded. During this period, the nurseries and neonatal intensive care units at Yokohama Municipal Citizens Hospital were practicing according to the 1996 and 2002 CDC guidelines with minor modifications. All pregnant women were screened for vaginal GBS colonization between 35 and 37 weeks' gestation. GBS-carrier pregnant women who were admitted for delivery were treated with empirical antibiotics consisting of intravenous ampicillin or clindamycin depending on the status of penicillin allergy. Mothers who received antimicrobial starting <4 h before delivery were defined as receiving inadequate IAP.

All neonates born from mothers who received inadequate IAP were closely monitored clinically. In addition, a CBC and C-reactive protein (CRP) levels were obtained on the first day of life. All test results of neonates born from mothers who received inadequate IAP were collected from the hospital computerized records and evaluated. CBC abnormalities were defined as either a total white blood cell (WBC) count <5,000/mm³ or >30,000/mm³ or a platelet count <150,000/mm³. CRP abnormalities were defined as ≥1.0 mg/dl⁹⁻¹².

Early-onset GBS infections were defined based on either the isolation of GBS from normally sterile sites, including blood and cerebrospinal fluid, or clinical signs of infection with colonization of GBS, as well as laboratory abnormalities. Colonization of GBS was defined

based on positive rectal or throat cultures.

Delivery at <37 weeks of gestation, amniotic membrane rupture ≥18 h before delivery, and intrapartum maternal temperature ≥38.0°C are considered as risk factors for EOGBS infection². We evaluated the effects of these factors on the occurrence of EOGBS infection.

Statistical analysis was performed to measure the reliabilities of CBC, CRP and clinical signs in diagnosing EOGBS infections. Descriptive statistical analysis was performed using the Statistical Package for the Social Sciences for Windows, release 20.0.0 (SPSS, Chicago, IL).

Results

In total, 1910 women delivered their babies at Yokohama Municipal Citizens Hospital from January 1, 2008 to April 1, 2010. Of the 1910, 273 (14%) were identified as GBS carriers, and the remainder were negative for maternal GBS screening. The records of these 273 carriers were reviewed. Of the 273, 69 (3.6%) received inadequate IAP, 196 (10%) received adequate IAP, and 9 (0.5%) received no IAP prior to delivery. Two of the 69 deliveries with inadequate IAP also showed prolonged rupture of the membranes, and a third was born prematurely. None of the mothers showed temperature ≥38.0°C during delivery.

According to our protocol, CBC count and CRP value were determined in all 69 neonates born from mothers who received inadequate IAP. The results are presented in Table I. Low platelet count and high WBC count were identified in 2 patients (2.9%) and 1 patient (1.4%), respectively. High CRP values were identified in 4 patients (5.8%). GBS-positive throat cultures and GBS-positive rectal cultures were identified in 3 patients and 4 patients, respectively. None of the blood cultures or cerebrospinal fluid cultures yielded positive results. Nine of the 69 neonates demonstrated clinical symptoms. Respiratory distress was noted in 6 patients (8.7%), tachycardia in 2 patients (2.9%), fever in 2 patients (2.9%), vomiting in 1 patient (1.4%), and irritability in 1 patient (1.4%). Five of 196 neonates who received adequate IAP demonstrated clinical symptoms. Respiratory distress was noted in 2 patients (1.0%), fever in 2 patients (1.0%), vomiting in 1 patient (0.5%), and tachycardia in 1 patient (0.5%). Neonates whose mothers

received inadequate IAP had a higher chance of developing clinical symptoms compared to those whose mothers received adequate IAP ($p=0.002$ on Fisher's exact test).

We found three EOGBS infections out of 1910 neonates during the study period (1.6 per 1000 live births) (Table II); all 3 neonates were born from GBS-positive mothers who received inadequate IAP. All 3 neonates presented with respiratory distress and CRP abnormalities. CRP abnormalities and respiratory distress served as reliable indicators for detecting EOGBS infections ($p=0.0004$ and $p=0.0001$ on Fisher's exact test) (Table III). None of the 3 neonates had CBC abnormalities, and all responded to antimicrobial treatment with no complications during the follow-up.

Discussion

None of the blood cultures was positive for GBS. Prior studies have reported lower rates of positive blood culture in patients who received inadequate IAP^{6,13,14}. Even though IAP is recommended to be implemented 4 h before delivery¹⁵, there is no clear evidence indicating that IAP implemented less than 4 h before delivery should be considered inadequate; this point is in need of further evaluation¹⁶⁻¹⁸.

We evaluated all neonates who received inadequate IAP, and found that CRP value and respiratory distress served as reliable indicators for detecting EOGBS infections (Table III). On the other hand, no neonates with EOGBS infection showed CBC abnormalities. CBC

within 6 h after birth has been previously reported as offering low sensitivity^{5,8,13,19,20}. In our study, most CBCs were performed within 6 h after birth, and the low sensitivity of CBC is consistent with those previous findings. In contrast, all three EOGBS infection cases showed CRP abnormalities. CRP has been reported previously as a reliable marker for neonatal infectious diseases^{11-13,21-23}. CRP values were measured at the same time as CBC measurements, which indicates that CRP is sensitive even during the early neonatal period.

All three EOGBS infection cases showed clinical symptoms, particularly respiratory distress (Table II). A wide variety of symptoms have been reported as manifestations of neonatal infectious disease, including hyperthermia, respiratory distress, anorexia, vomiting, and jaundice²⁴. Respiratory distress is reported as one such common symptom, although the mechanisms underlying the relationship between infection and respiratory distress are unclear.

We did not obtain routine blood test or culture from neonates whose mothers received adequate IAP. The guideline clearly says that no routine diagnostic testing is recommended in neonates who received adequate IAP². Thus, we concluded that performing routine blood test or culture was ethically unacceptable. Nonetheless, neonates whose mothers received adequate IAP had a lower chance of developing clinical symptoms or EOGBS infection. This is

Table I. White Blood Cell (WBC) Count, Platelet (PLT) Count, and C-Reactive Protein (CRP) Values of 69 Neonates Who Received Inadequate IAP

	Standard deviation	Median (range)	Abnormal measures (%)
WBC (/mm ³)	5574	17900 (5100-34300)	1 (1.4)
PLT (/mm ³)	60177	265000 (120000-416000)	2 (2.9)
CRP (mg/dl)	0.55	0.1 (0-3.8)	4 (5.8)

IAP: Intrapartum antibiotic prophylaxis.

Table II. Clinical Characteristics of EOGBS Infection Cases

Case	Gestational age (wk) / Birth weight (g)	Clinical symptoms	Positive culture	WBC (/mm ³)	CRP (mg/dl)
1	39/3100	Respiratory distress	Throat, rectum	5100	1.0
2	37/2880	Respiratory distress	Rectum	13490	3.8
3	39/3490	Respiratory distress, fever	Throat, rectum	12900	1.4

CRP: C-reactive protein. EOGBS: Early-onset group B streptococcal. WBC: White blood cells.

Table III. Comparison of EOGBS Infection Cases and Non-EOGBS Infection Cases

	EOGBS (n=3)	Non-EOGBS (n=66)	<i>p</i> *
Respiratory distress	3 (100%)	3 (5%)	0.0004
Risk of infection	0 (0%)	3 (5%)	1
CBC abnormality	0 (0%)	3 (5%)	1
CRP abnormality	3 (100%)	1 (2%)	0.0001

* Fisher's exact test.

CBC: Complete blood count. CRP: C-reactive protein. EOGBS: Early-onset group B streptococcal.

consistent with previous literature suggesting that adequate IAP is more effective than inadequate IAP in preventing EOGBS infection²⁵.

Chorioamnionitis is an important risk factor for EOGBS infection^{2, 26, 27}. The diagnosis of chorioamnionitis is usually made clinically based on the symptoms, including maternal fever in labor. In addition, delivery at <37 weeks of gestation and amniotic membrane rupture ≥18 h before birth are considered as risk factors for EOGBS infection according to the current guideline². In the present study, none of the three EOGBS infection cases displayed any of these risk factors. However, placental histology in Case 3 (Table III) showed acute chorioamnionitis. We reviewed the maternal record again and found that the mother had a marginal fever of 37.9°C during labor. Although isolated low-grade fever in labor is frequently associated with epidural labor analgesia²⁸, performing a thorough clinical evaluation is important to rule out chorioamnionitis.

The incidence of EOGBS infection in the current study was higher than previously reported. This is possibly due to the wider diagnostic criteria of EOGBS infection in the current study. Isolation of bacteria from a central body fluid represents the diagnostic gold standard and is the most specific method used to diagnose neonatal sepsis. Unfortunately, clinical signs of sepsis in neonates can be non-specific and often manifest in the absence of positive culture findings. The International Pediatric Sepsis Consensus Conference recently published that sepsis should be considered whenever generalized systemic inflammatory response is seen with organ dysfunction, which can be traced to infection²⁹. We thus decided to diagnose EOGBS infection without relying solely on positive blood cultures.

Pain stimuli to neonates can reportedly cause

both short- and long-term alterations in pain perception^{30,31}. In addition, a longer hospital stay results in higher costs. Unnecessary diagnostic tests and empirical treatment for neonates should thus be avoided.

Our current study was limited in the small number of patients enrolled. However, because of the small number of staff physicians, data were collected relatively homogeneously and the results appear reliable. The aim of this study was not only to reveal the predictors of EOGBS infection among neonates born to mothers who received inadequate IAP, but also to propose our method as a model to be utilized in future multi-center studies. We believe the results of this study provide a guide for future studies.

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