NEONATAL GROUP B STREPTOCOCCUS SEPSIS: A MULTICENTER STUDY IN THAILAND

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Abstract. Invasive group B Streptococcus (GBS) is the most common cause of early-onset neonatal sepsis worldwide, but there are only a few studies of the incidence of neonatal GBS sepsis in Thailand. Routine intrapartum antibiotic prophylaxis is not recommended in Thailand. We aimed to determine the incidence and mortality of GBS sepsis in a multicenter study in Thailand in order to inform GBS prevention and control strategies. We retrospectively reviewed the medical records of neonates to identify those with GBS sepsis at 9 multi-level neonatal care units in Thailand. GBS sepsis was classified by a history of having a blood or cerebrospinal fluid (CSF) culture positive for GBS. The incidence of GBS sepsis (either blood or CSF culture positive for GBS) was 0.12/1,000 live births (33/278,291); of whom 29 (88%) had a positive blood culture for GBS, 2 (6%) had a positive CSF culture for GBS and 2 (6%) had positive blood and CSF cultures for GBS. Twenty-six neonates had early-onset (≤6 days after birth) sepsis and 7 neonates had late-onset (≥7 days after birth) sepsis. The medians [interquartile ranges (IQR)] for gestational age and birthweight were 38 (5) weeks and 2,760 (1,080) grams. Seven neonates (21%) died. In conclusion, the incidence of neonatal GBS sepsis in our multicenter study from Thailand was lower than in some other regions in the world but the mortality rate was high. Further studies are needed to determine if screening for GBS among pregnant woman and the use of intrapartum antibiotic prophylaxis are warranted in Thailand due to the high mortality rate.

Keywords: newborn, neonatal intensive care, sepsis, *Streptococcus agalactiae*, Group B Streptococcus

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INTRODUCTION

Invasive group B Streptococcus (GBS) disease is a leading cause of infant mortality and morbidity worldwide. Before the advent of GBS screening and treatment, GBS was the most common cause

of early-onset neonatal sepsis (Bizzarro *et al*, 2005; Stoll *et al*, 2011). Vertical and horizontal transmission of GBS can take place from the mother's colonized vagina to the newborn at delivery in early-onset GBS (EOGBS; 0-6 days) and is associated with the environment or infected breast milk in late-onset GBS (LOGBS; 7-89 days) (Morinis *et al*, 2011; Filleron *et al*, 2014; Le Doare and Kampmann, 2014).

The mean incidences overall of GBS, EOGBS, and LOGBS sepsis among infants aged 0-89 days were reported in a meta-analysis to be 0.53, 0.43, and 0.24 cases/1,000 live births, respectively (Edmond *et al*, 2012). Intrapartum antibiotic prophylaxis (IAP) has lowered the incidence of EOGBS from 0.75 cases/1,000 live births among patients who did not receive prophylaxis to 0.23 cases/1,000 live births among those who did (Edmond *et al*, 2012).

Southeast Asia has the lowest incidence of neonatal GBS sepsis in the world (Edmond *et al*, 2012). In Thailand, the current incidence of neonatal GBS sepsis is unclear because there is no mandatory reporting system. Routine IAP is not recommended in Thailand. This study investigated the incidence, risk factors, outcomes and the case fatality rate (CFR) for neonatal GBS sepsis in multiple centers in Thailand in order to inform GBS prevention and control strategies.

MATERIALS AND METHODS

Study sites

This study was conducted at nine neonatal care centers in Thailand: Songklanagarind Hospital and Songkhla Hospital in Songkhla Province, Thasala Hospital and Thung Song Hospital in Nakhon Si Thammarat Province, Nakhon Pathom Hospital in Nakhon Pathom Province, Vachira Phuket Hospital in Phuket Province, Phatthalung Hospital in Phatthalung Province, Trang Hospital in Trang Province, and Khuan Kalong Hospital in Satun Province (1 university hospital, 3 tertiary level hospitals, 3 secondary level hospitals, and 2 primary level hospitals).

Study subjects

The study subjects were identified by retrospective reviewing the hospital medical records, and microbiology and laboratory records at each hospital. All patients aged <28 days with a diagnosis of GBS sepsis (having either blood or CSF culture positive for GBS) admitted from January 1, 1991 to December 31, 2015 where medical records were available were included in the study. Each study hospital had a different data collection period; however, the data were collected for as long as possible from completed medical records. Data obtained from the charts were: history of prolonged rupture of membranes (>18 hours), chorioamnionitis (intrapartum fever >38°C and at least two of the following: maternal leukocytosis (>15,000 cells/mm^3), maternal tachycardia (>100 beats/minute), fetal tachycardia (>160 beats/minute), maternal uterine tenderness and/or amniotic fluid with a foul odor, and neonatal data (demographics, clinical manifestations, antimicrobial use, antimicrobial susceptibilities, and outcomes). The study was approved by the Ethics Committee at the Faculty of Medicine, Prince of Songkla University and at each hospital where the study was conducted.

Infants included in the study were those who had a history of a positive blood or cerebrospinal fluid (CSF) culture for GBS. The clinical characteristics and outcomes were reported only for study subjects. The terms "preterm", "very preterm", and "extremely preterm" were

defined as gestational ages (GA) of 32-36, 28-31, and <28 weeks, respectively. "Very low birthweight" (VLBW) and "extremely low birthweight" (ELBW) were defined as birthweights (BW) of 1,000-1,499 and <1,000 grams, respectively. GBS sepsis was defined as a patient who had a positive blood and/or a CSF culture for GBS. GBS was identified based on routine laboratory standards at the study hospitals. The onset of sepsis was defined as the time in which a culture positive for GBS was obtained. The definitions of EOGBS and LOGBS infections were onset of sepsis ≤6 days and ≥7 days, respectively. Inadequate empiric antimicrobial therapy was defined as the use of antibiotics for >48 hours after the blood cultures were obtained in which those antibiotics did not cover the microorganism causing the bacteremia or the administration of antibiotics that failed to cover resistant microorganisms. Inadequate antimicrobial therapy included the absence of a prescribed antimicrobial agent directed against the specific class of recovered microorganisms and/or administration of antimicrobial agents to which the microorganism responsible for the infection was resistant (Thatrimontrichai *et al*, 2013).

Outcomes

The primary outcome was to determine the incidence of neonatal GBS sepsis, including EOGBS and LOGBS among the study subjects. The secondary outcomes were the characteristics, susceptibilities, outcomes, and risks for mortality due to GBS sepsis among the study subjects.

Statistical analysis

The R program (R Core Team, 2014) and Epicalc package (Chongsuvivatwong, 2012) were used to develop a database for categorical and continuous variables. Categorical variables are presented as frequencies and percentages and were compared using the χ^2 test or Fisher's exact test. Continuous variables are presented as medians and interquartile ranges (IQR) and were compared using the Mann-Whitney *U* test. All *p*-values were 2 tailed. A *p*-value <0.05 was considered statistically significant.

RESULTS

Thirty-three GBS sepsis infants were born at the study hospitals (inborn) and 8 were transferred to the study hospitals (transferred). The incidence of GBS sepsis among neonates at the study sites was 0.12/1,000 live births (33/278,291 live births) (Table 1). The incidence of EOGBS sepsis was 0.09/1,000 live births (25/278,291 live births). Of the combination of the 41 "inborn" and "transferred" patients, 33 (80%) had complete medical records and were evaluated for characteristics and outcomes. Of these 33 cases, 29 (88%), 2 (6%), and 2 (6%) neonates had positive GBS cultures from the blood only, CSF only, and both blood and CSF, respectively. Complete medical records were available for 26 EOGBS and 7 LOGBS cases. The medians (IQRs) for gestational age (GA) and birth weight (BW) were 38 (5) weeks and 2,760 (1,080) grams, respectively; 70% (23/33) of the cases occurred at full-term (≥37 weeks gestation). The medians (IQRs) for the Apgar scores at 1 and 5 minutes of life were 9 (1) and 10 (1), respectively. Sixteen (49%), 21 (64%), and 23 (70%) neonates had onset of GBS sepsis within 24, 48, and 72 hours, respectively. The medians (IQRs) for the onset of EOGBS and LOGBS sepsis were 12 hours (2 days 20 hours) and 20 days 23 hours (21 days 2 hours), respectively. The medians (IQRs) for the length of stay and hospital cost were 8 (11) days and USD 754.4 (641.1).

Table 1
Incidences of group B Streptococcus (GBS) and early-onset GBS (EOGBS) sepsis in Thailand.

Hospital and years data collected	Incidence of GBS sepsis among study infants per 1,000 live births (*n*)	Incidence of EOGBS sepsis among study infants per 1,000 live births (*n*)
Songklanagarind Hospital (1991-2015)	0.10 (7/71,347)	0.10 (7/71,347)
Songkhla Hospital (2007-2015)	0.11 (4/37,950)	0 (0/37,950)
Thasala Hospital (2010-2015)	0 (0/9,324)	0 (0/9,324)
Thung Song Hospital (2010-2015)	0.17 (4/23,966)	0.13 (3/23,966)
Nakhon Pathom Hospital (2010-2015)	0.17 (5/29,200)	0.10 (3/29,200)
Vachira Phuket Hospital (2007-2015)	0.12 (6/49,473)	0.12 (6/49,473)
Phatthalung Hospital (2007-2015)	0.15 (6/40,540)	0.12 (5/40,540)
Trang Hospital (2012-2015)	0.08 (1/13,228)	0.08 (1/13,228)
Khuan Kalong Hospital (2008-2015)	0 (0/3,263)	0 (0/3,263)
Overall incidence in this study	0.12 (33/278,291)	0.09 (25/278,291)

The reported antibiogram depended on routine and available antibiotic discs at each study hospital. Tested isolates were susceptible to erythromycin (81%), ampicillin (88%), clindamycin (88%), penicillin (91%), and vancomycin (100%). All non-susceptible to ampicillin patients were from Songklanagarind Hospital (intermediate susceptible results were reported in 1999 and 2003, and resistant results were reported in 2012). The numbers of patients with inadequate empiric antimicrobial therapy and inadequate antimicrobial therapy were 2 neonates and 1 neonate, respectively. The CFR overall and among preterm neonates were 21% (7/33) and 50% (5/10), respectively. The CFR within 24 hours, for EOGBS sepsis, and for LOGBS sepsis were 31% (5/16), 23% (6/26), and 14% (1/7), respectively. A lower BW and younger GA were associated with significantly higher mortality and prematurity [Odds ratio (OR) = 10.5, 95% Confidence interval (CI) : 1.6-70.8, $p = 0.02$) and ELBW (OR = 18.9, 95% CI : 1.5-250.0, $p = 0.02$) (Table 2). Among patients who did not survive, the median (IQR) daily hospital cost was significantly higher than among those who did survive [USD 248.9 (346.0) *versus* USD 60.4 (42.7), $p < 0.001$].

DISCUSSION

In the United States, the incidence of neonatal GBS infection declined dramatically from 1.7/1,000 live births in 1990 to 0.34-0.37/1,000 live births in 2004-2008 (Verani *et al*, 2010). Southeast Asia had the lowest incidence of GBS cases (0.02 cases/1,000 live births) in the world (Edmond *et al*, 2012). There are only 4 previous studies (2 prospective studies, one retrospective and one case series) of neonatal GBS sepsis in Thailand among patients without IAP used (Yossuck and Preedisripipat, 2002; Al-Taiar *et al*, 2013; Thatrimontrichai *et al*, 2014; Villanueva-Uy *et al*, 2015). Five studies (3 prospective studies, one retrospective and one cross sectional study) found no GBS sepsis (Janjindamai *et al*, 1998;

Table 2
Univariate analysis of risk factors and outcomes associated with death among study subjects with Group B Streptococcus (GBS) infection.

Risk factors	Survival	Non-survival	*p*-value
Male, *n* (%)	9/26 (34.6)	4/7 (57.1)	0.4
Gestational age (weeks), median (IQR)	38.5 (2)	32 (13)	0.006
Preterm, *n* (%)	5/26 (19.2)	5/7 (71.4)	0.02
Very preterm, *n* (%)	3/26 (11.5)	3/7 (42.9)	0.09
Extremely preterm, *n* (%)	2/26 (7.7)	3/7 (42.9)	0.05
Birth weight (grams), median (IQR)	2,952 (855)	1,650 (1,350)	0.003
Very low birth weight, *n* (%)	2/26 (7.7)	3/7 (42.9)	0.05
Extremely low birth weight, *n* (%)	1/26 (3.8)	3/7 (42.9)	0.02
Appropriate for gestational age, *n* (%)	20/26 (76.9)	7/7 (100)	0.3
Inborn, *n* (%)	23/26 (88.5)	6/7 (85.7)	1.0
Vaginal delivery, *n* (%)	19/26 (73.1)	5/7 (71.4)	1.0
Apgar score at 5 minutes, median (IQR)	9 (0)	5 (8)	0.06
Apgar score at 10 minutes, median (IQR)	10 (1)	5 (8)	0.1
Onset of sepsis (day:hour), median (IQR)	1:2 (8:8)	0:3 (2:8)	0.3
Early-onset GBS, *n* (%)	20/26 (76.9)	6/7 (85.7)	1.0
Inadequate empiric antimicrobial therapy, *n* (%)	1/26 (3.8)	1/7 (14.3)	0.4
Inadequate antimicrobial therapy, *n* (%)	1/26 (3.8)	0/7 (0)	1.0
Length of stay (days) , median (IQR)	9 (10)	4 (5)	0.009
Hospital cost (USD), median (IQR)	705.5 (697.9)	1,132.2 (1,182.7)	0.3
Daily hospital cost (USD), median (IQR)*	60.4 (42.7)	248.9 (346.0)	<0.001

*USD1 ≈ 30 Baht.

Werawatakul *et al*, 2001; Kovavisarach *et al*, 2007; Tiskumara *et al*, 2009; Herbert *et al*, 2015). The pooled mean (range) incidence of GBS sepsis in this study was 0.12 (0.08-0.17)/1,000 live births. The pooled mean incidence of GBS sepsis cases among all the previous studies from Thailand including this study was 0.15 (0.12-0.24)/1,000 live births (Table 1), similar to studies from Bangladesh (0.10/1,000 live births; Darmstadt *et al*, 2009) and Japan (0.13/1,000 live births; Chang *et al*, 2014).

The prevalence of maternal GBS colonization in Thailand has been reported to be 12-18% (Thinkhamrop *et al*, 2003; Tor-Udom *et al*, 2006; Kovavisarach *et al*, 2007; *idem*, 2008; Herbert *et al*, 2015). One study reported a prevalence of 6% (Werawatakul *et al*, 2001). However, lower prevalence rates of GBS colonization have been reported from India (2.3-2.5%) (Kulkarni *et al*, 2001; Sharmila *et al*, 2011), Korea (6%) (Uh *et al*, 1997), Iran (9%) (Namavar Jahromi *et al*, 2008), and Turkey (9%) (Eren *et al*, 2005). Higher prevalence rates of colonization have been reported from the United States (19-26%) (Regan *et al*, 1991; Campbell *et al*, 2000), Poland (19%) (Krasnianin *et al*, 2009), Germany (21%) (Kunze *et al*, 2011), Switzerland (21%) (Rausch *et al*, 2009), Croatia (25%) (Muller-Vranjes *et al*, 2011), Saudi Arabia (32%) (Zamzami *et al*, 2011), Trinidad (33%) (Orrett, 2003) and Denmark (36%) (Hansen *et al*, 2004). Heavy maternal colonization, intrapartum fever, African ethnicity, and

not receiving IAP were associated with GBS transmission among Italian neonates born to women who tested positive for GBS (Berardi *et al*, 2014). Vaginal-rectal screening for GBS and IAP are not routine practices in Thailand.

Seventy percent of GBS sepsis cases in our study were full-term neonates, similar to a report from the United States (Phares *et al*, 2008). The percentages of neonates who had onset of GBS sepsis within 24 and 48 hours of birth (49% and 64%) in our study were lower than a previous study in the United States during 1999-2005 (72% and 95%, respectively) (Phares *et al*, 2008).

The CFR in our study (21%) was similar to a previous report from developing countries including 8 studies from sub–Saharan Africa, 2 from the Middle East, 5 from South Asia, 2 from Southeast Asia, and 3 from Latin America (20%; range 10-60%) (Dagnew *et al*, 2012). The CFR for the pooled mean overall, EOGBS, and LOGBS from Thailand at Siriraj Hospital (Yossuck and Preedisripipat, 2002), Siriraj Hospital and Queen Sirikit National Institute of Child Health (Villanueva-Uy *et al*, 2015), and in this study were 26% (14/54), 30% (13/43) and 9% (1/11), respectively. However, the CFR for the pooled mean overall, EOGBS, and LOGBS from a systematic worldwide review were 9.6%, 12.1%, and 6.8%, respectively (Edmond *et al*, 2012). The overall CFR in our study is similar to other developing countries but higher than the global data. The CFR in low-income countries (12.6%) has been reported to be 3 times higher than in high-income countries (4.6%) (Edmond *et al*, 2012). The CFR among preterm infants has been reported to be 8 times and 3 times that of full-term cases for EOGBS and LOGBS infections (Phares *et al*, 2008). A lower GA and lower BW (Table 2) were associated with increased mortality and a preterm neonate weight of <1,000 grams in our study. The Apgar score and time to onset of sepsis were not significantly different between the survival and non-survival groups.

This study had limitations. First, it was a retrospective design that used hospital-based data. The number of EOGBS sepsis cases probably does represent the true number of cases but the number of LOGBS sepsis cases may not be accurate because some neonates may not have returned to the study hospital for treatment. We only studied cases aged ≤28 days; therefore, we missed the cases that presented after 28 days. Most of the study hospitals in our study had incomplete medical records. Each study hospital collected different data. Diseases and health care systems change over time and it is difficult to compare data and make conclusions. Second, lumbar punctures and post-mortem examinations were not performed in all the sepsis cases due to their being too unstable to perform a lumbar puncture. Therefore, the number of meningitis cases may be underreported. Routine cranial ultrasound and CT imaging were not performed due to the unavailability of portable ultrasound equipment and no pediatric radiologists. Long term neurodevelopmental assessments were not conducted in the survival group. The serotypes of GBS were not determined in this study.

Serotype III (49%) is the most frequently identified serotype worldwide followed by serotypes Ia (23%), V (9%), Ib (7%), and II (6%) (Edmond *et al*, 2012). One study from Thailand found serotypes III and VI (Villanueva-Uy *et al*, 2015). Another study conducted among a refugee population along the Thai-Myanmar border examining GBS colonization among pregnant women found serotype II to be

the most common serotype, followed by serotypes Ia, VI, III, V, VII, and IV (Turner *et al*, 2012). In one study from China serotype II was the most common serotype identified (Johri *et al*, 2013).

There are some implications from our study. The decision to give IAP in our study population is unclear due to low incidence of GBS but the high CFR in this population. Preterm labor and ELBW neonates with GBS sepsis were at high risk for mortality and should be monitored closely for GBS. The combination of ampicillin and gentamicin for empiric antimicrobial therapy in a study from Thailand to treat possible GBS sepsis should be considered since 12% of isolates were reported to be resistant to ampicillin in one study (Thatrimontrichai *et al*, 2013).

In summary, we found a low incidence of GBS sepsis among study patients compared to other regions in the world without routine IAP. However, the CFR among GBS cases in our study was similar to other developing countries and higher than other countries. The percentages of preterm neonates and ELBW infants and the daily hospital costs of GBS sepsis patients were higher in the infants that did not survive than in the infants that did survive.

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