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POSTNATAL PENICILLIN PROPHYLAXIS OF EARLY-ONSET GROUP B STREPTOCOCCAL INFECTION IN TERM NEWBORNS: A PRELIMINARY STUDY

Lucia Stillova[a], Zuzana Strechova[a], Katarina Matasova[a], Hana Kolarovszka[a], Kristina Bodova[b], Juraj Stilla[c], Mirko Zibolen[a]

[a] *Clinic of Neonatology*
[b] *Clinic of Obstetrics and Gynecology*
[c] *Clinic of Stomatology and Maxillofacial Surgery*
Jessenius Faculty of Medicine, Comenius University, Faculty Hospital of Martin, Martin, Slovakia
e-mail: luciastillova@gmail.com

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Background: Early-onset group B Streptococcal disease (EOGBSD) is a serious but preventable neonatal infection. Maternal intrapartum antibiotic prophylaxis (IAP) does not prevent all cases of the disease. Management of asymptomatic neonates of GBS colonized mothers is problematic.

Aims: The objective of this prospective study was to determine whether administration of intramuscular penicillin at birth to a strictly defined group of term newborns of GBS colonized mothers is an effective and safe method to prevent EOGBSD.

Methods: A protocol for management of full-term infants born to GBS colonized mothers was created. Either an abnormality of blood count or presence of more than one obstetric risk factor were chosen as the indication criteria for administering postnatal antibiotic prophylaxis (PAP).

Results: The study sample consists of 250 newborns (11.5 % of all term infants). PAP was administered in 39 cases. Indication criteria included leucocytosis in 37 cases, leucopenia in 1 case and obstetric risk factors in 1 case. There was no case of clinically manifest infection, and no case of sepsis either suspect or proven.

Conclusions: The authors suggest that the strategy of selective PAP using penicillin, may be an effective and safe method in order to reduce morbidity and mortality from streptococcal infections. They recommend a combination of IAP and selective PAP.

INTRODUCTION

Early-Onset Group B Streptococcal Disease (EOGBSD) is a very serious but preventable infection in newborns. *Streptococcus agalactiae* or Lancefield group B Streptococcus (GBS) emerged dramatically in the 1970s as the leading cause of invasive neonatal infection[1]. At our clinic there were 11.6 % of preterm newborns affected with early-onset infection and the culture results showed that the most frequent pathogen found in mothers was GBS (16.2 %)(ref.[2-4]).

EOGBSD or perinatal form of GBS disease, accounts for approximately 80 % of neonatal GBS cases[5]. It typically occurs within the first 24 hours of life[6], with fulminant sepsis or pneumonia and rarely with meningitis. The incidence of EOGBSD varies in different parts of world from 0.17 or 0.5 to 4 cases per 1,000 live births[7,8]. Although early-onset neonatal sepsis is associated with severe course and high case fatality rate (5–20 %)[9], there is no appropriate laboratory marker for its early diagnosis. It is difficult to make a reliable diagnosis of EOGBSD, because of the stereotypical way in which newborns react to various insults[10]. Infection is defined as an inflammatory response to the presence of microorganisms or to their invasion to normally sterile sites of the host; sepsis as a systemic inflammatory response to existing infection[11]. Early onset infection is defined as infection presenting within the first 72 hours of life[12]. The GBS infection is categorized as probable when there is isolation of GBS from surface swabs in a symptomatic infant with laboratory evidence of infection or radiological evidence of pneumonia. Definite GBS sepsis is diagnosed when there is isolation of GBS either from the blood or cerebrospinal fluid in a symptomatic neonate[8].

The major risk factor for EOGBSD in infants is maternal intrapartum GBS colonization. Women with prenatal GBS colonization are 25 times more likely than women with negative prenatal cultures to deliver infants with the disease[13]. The prevalence of recto-vaginal colonization among pregnant women ranges from 15 to 40 %[14]. The colonization is dynamic, and mostly asymptomatic. Carriers are identified by bacteriological testings. The rate of vertical transmission in neonates born to women colonized with GBS at the time of delivery ranges from 30 to

70 %[6,7]. Although most newborns of GBS colonized mothers become colonized on skin or mucous membranes, they remain asymptomatic; among these, 1 to 4 % rapidly develop clinical infection. In conclusion, there is reported an attack rate of 1–2 % invasive GBS disease in infants born to colonized mothers[8].

Because GBS infection is a major cause of neonatal illness and death, several preventive strategies have been evaluated. The reference recommendations were published by the CDC in 1996(ref.[15]). Since then, there has been a reported 70 % reduction in EOGBSD but no decrease in late-onset neonatal GBS disease[1]. The CDC guidelines were reevaluated and updated in 2002(ref.[13]). The recommended strategy is based solely on a universal prenatal screening-approach, with integration of a risk-based approach if necessary. Universal screening for GBS is appropriate, since many GBS colonized infants had no identifiable maternal risk factors[16]. Maternal intrapartum antibiotic prophylaxis (IAP) is currently considered to be the most effective strategy in preventing neonatal GBS disease, and it is the method of choice. All patients should be screened for GBS at 35 to 37 weeks with vaginal and rectal cultures. If a patient is positive, she is treated in labor.

Maternal IAP will not prevent all cases of early-onset GBS disease[5]. In the case that intrapartum antibiotics are not given despite an indication (e.g., delivery occurred precipitously before antibiotics could be administered to a GBS-positive woman), insufficient data are available on which to recommend a single management strategy for newborn[13]. The complete absence of EOGBSD was reported as an unexpected benefit of a policy of routine administration of intramuscular penicillin to prevent gonococcal ophthalmia[17]. Giving an injection of penicillin immediately after birth to newborn babies routinely has been proposed as another way of preventing GBS infection[14]. Some centers administer intramuscular penicillin to asymptomatic infants within 1 hour after birth, based on results of observational studies showing declines in EOGBSD[13]. The infants who received penicillin prophylaxis had a decreased incidence of clinical sepsis and of GBS positive blood culture[18]. There was also reported parenteral administration of penicillin for at least five days to infants born to mothers with genital carriage of GBS, irrespective of whether the newborns were symptomatic at birth or not[8]. However, it is important to accept the fact, that routine use of antimicrobial prophylaxis for newborns whose mothers received IAP is not recommended[5,13].

Our objective is to determine whether the administration of intramuscular penicillin at birth to a defined group of term newborns of GBS colonized mothers is an effective and safe method to prevent morbidity and mortality from EOGBSD. The aim of the prospective study is to design an optimal strategy for administering postnatal antibiotic prophylaxis (PAP), and to assess the administering of IAP and PAP and their effectiveness in the clinical setting of our hospital.

METHODS

The obstetric program in our hospital includes a GBS prevention policy based on the universal prenatal screening-based strategy with the integration of risk-based options when necessary. In order to prevent further neonatal GBS disease, our management of newborns born to GBS colonized mothers is based on information about administering IAP and information about obstetric risk factors.

We chose GBS positive culture results at 35 to 37 weeks of gestation, and, at the same time, either the total number of newborns' leucocytes at birth more than 25, or less than 8 x 10^9 per liter, or the presence of more than one obstetric risk factor, as the indication criteria for administering PAP. For the postnatal prophylaxis we used intramuscular penicillin in a daily dose of 80 000 units per kilogram of newborn's weight, applied every 12 hours. After the third dose of penicillin, the blood count was checked, and if it returned to normal levels, PAP was terminated after the third dose of penicillin. If the blood count did not return to normal levels, penicillin was continued. If there was a positive blood culture result, the prophylaxis had to be changed into treatment. If sepsis was suspected based on clinical and laboratory evaluations, empirical antibiotic therapy, using ampicillin and gentamicin, should be started. The reason for the antibiotic therapy was the possibility of non-GBS sepsis.

We created a protocol for the management of a term infant born to a GBS colonized mother. We analyze weight at birth, Apgar score, administrating of IAP and its duration, newborn's blood cell count at birth and after the third dose of postnatal penicillin, clinical signs, amniotic water culture result, newborn's outer ear canal culture result, and maternal risk factors such as intrapartum fever (38 °C or higher), prolonged rupture of membranes (18 hours or more), previous infant with invasive GBS infection, and urinary tract infection during the current pregnancy.

The risk for GBS sepsis was assessed according to the Swiss Society of Neonatology. Full-term infants of GBS colonized mothers, without any additional risk factors and without IAP, are considered to be at risk for GBS sepsis 6 / 1000. If there are any additional risk factors, the risk increases 12.5 times. If the duration of IAP is longer than 4 hours, it reduces the risk 33 times (the risk is 0.18 / 1000)(ref.[19]). It is not known how much PAP reduces the risk for the disease.

RESULTS

The prospective study was started in September 2004, and ended in July 2006. The study sample consists of 250 newborns with appropriate postnatal adaptation. The study group accounted for 11.5 % of all term infants born in our hospital within that time period. The mean birth weight of the study group was 3441 grams (+/– 459 grams). The mean gestational age was 40.2 gestational weeks (+/– 1.0 weeks).

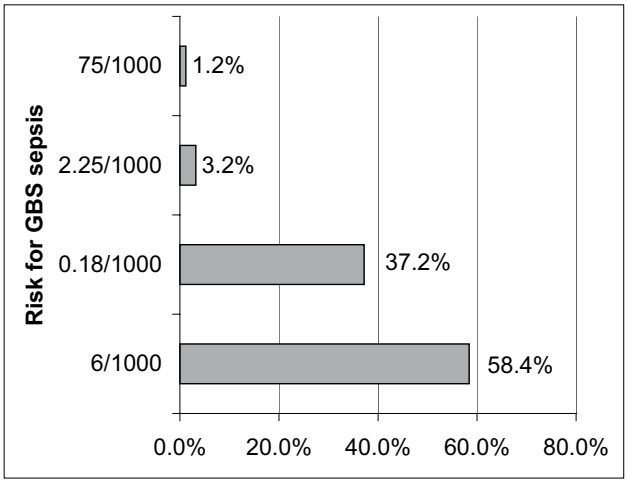


Fig. 1. Distribution of risk for GBS sepsis in the study group.

In our study group there were 146 newborns at risk for GBS sepsis 6 / 1000. Ninety-three neonates were at risk 0.18 / 1000, because of the administration of IAP. There were 8 neonates at risk 2.25 / 1000, because of additional risk factors and IAP at the same time. Three newborns were at risk 75 / 1000, because of prolonged rupture of membranes or intrapartum fever, and no IAP or IAP of unsatisfactory duration. In these infants, to whom PAP was not administered because of adequate blood count, there were no signs of infection found and negative culture results. (Fig. 1)

There were 11.5 % of all term newborns born to GBS colonized mothers. Out of 250 infants, PAP was administered in 39 cases. The indication criteria included leucocytosis in 37 cases, leucopenia (4.6 x 10^9 per liter) in 1 case, and two additional risk factors such as prolonged rupture of membranes and intrapartum fever in the mother in 1 case (Fig. 2). The mean count of leucocytes after the third dose of parenteral penicillin was in this subset of neonates 19.0 x 10^9 per liter (+/– 4.3 x 10^9 per liter), the mean count of thrombocytes after the third dose of penicillin was 292.4 x 10^9 per liter (+/– 61.2 x 10^9 per liter). In 30 out of 38 newborns with altered blood count, the total number of leucocytes returned to normal after three doses of penicillin. In 8 newborns the PAP had to be prolonged because the blood counts did not normalize. Negative culture results and no signs of infection were found in these eight infants. Four of these neonates were at risk for GBS sepsis 0.18 / 1000 because their mothers received IAP, one was at risk 2.25 / 1000 because of IAP and prolonged rupture of membranes, and three were at risk 6 / 1000.

Out of the 39 newborns with PAP, in 19 of their mothers no IAP was administered. According to our criteria, PAP was administered in 20 infants, although their mothers received antibiotic prophylaxis. (Fig. 3)

Amniotic water culture results were GBS positive in 13.4 % of newborns, 96.8 % of these were infants at high risk for sepsis (6 / 1000). Ear culture results were positive in 19.2 % of newborns, 91.1 % of these were at high risk for sepsis. (Fig. 4)

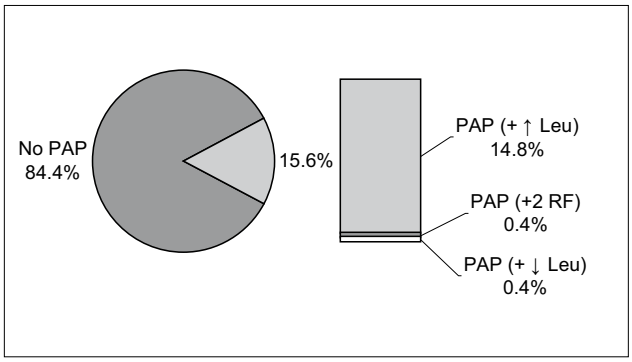
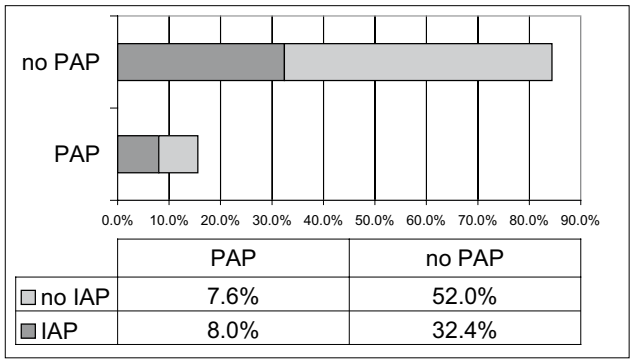


Fig. 2. Administration of postnatal antibioprophylaxis (PAP) and the indication criteria used.



	PAP	no PAP
no IAP	7.6%	52.0%
IAP	8.0%	32.4%

Fig. 3. Distribution of administration of intrapartum antibioprophylaxis in mothers (IAP) and postnatal antibioprophylaxis in their newborns (PAP).

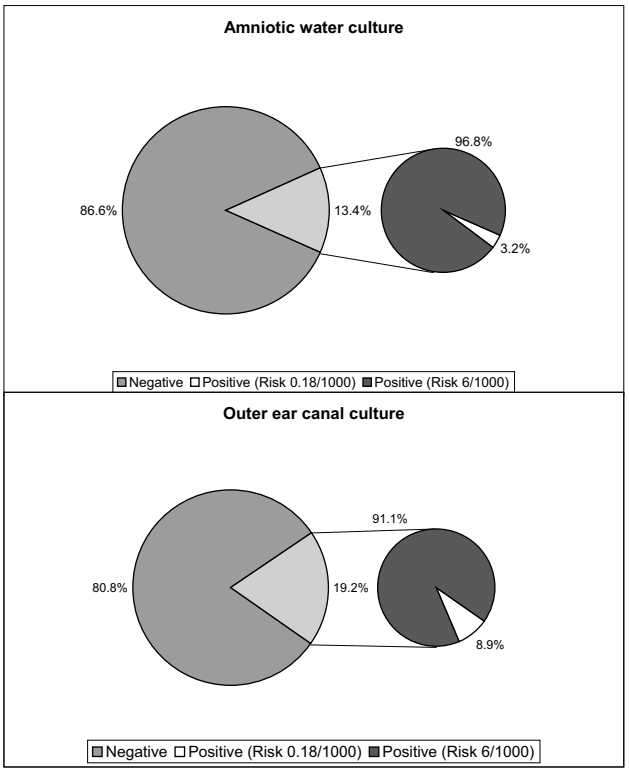


Fig. 4. Microbiological examination: amniotic water culture results and newborns' outer ear canal culture results.

In the study group, no clinical signs of infection were observed. Abnormalities of blood cell count were found in 38 infants- leucocytosis was a part of indication criteria for PAP in 37, leucopenia (4.6 x 10^9 per liter) in 1. No thrombocytosis or thrombocytopenia were found. At birth, the mean count of leucocytes in the study group was 19.1 x 10^9 per liter (+/– 5.7 x 10^9 per liter), the mean count of thrombocytes was 268.2 x 10^9 per liter (+/– 62.3 x 10^9 per liter).

In the study group consisting of 250 neonates at risk for EOGBSD, there was no case of probable GBS infection with clinical manifestation, and there was no case of definite GBS sepsis.

DISCUSSION

The management of symptomatic neonates born to GBS colonized mothers is well-defined. By contrast, the management of asymptomatic neonates is problematic. There is only an approach for empiric management of infants with suspected sepsis born to GBS colonized women who received or should have received IAP[5,13]. It is important to begin antimicrobial therapy, using ampicillin and gentamicin, as soon as possible if sepsis is suspected. The prognosis of patients with GBS sepsis depends mainly on the time when treatment is begun, and on comprehensive intensive care[6]. A complete clinical evaluation is irreplaceable, it is important to assess the clinical signs in a comprehensive way. As the response to various insults in the neonatal period is atypical, it is not enough to rely on clinical signs and merely observe an infant at risk for sepsis. Therefore, we prefer postnatal prophylaxis of the EOGBSD as it is such a serious neonatal infection.

The increased use of IAP for preterm delivery has created a shift in the disease towards term infants[20]. Most infants affected are full-term infants, even if the attack rate is higher in premature and low weight neonates[7]. Term infants account for approximately 70 % of cases of early-onset GBS septicemia in neonates[5]. This is why our study group consisted of term infants.

Current strategies used to prevent EOGBSD focus on maternal IAP based on the universal culture screening approach. It remains we do not know the GBS colonization status of all pregnant women who come to our hospital to give birth. For this reason the newborns included in our study are not newborns of all GBS colonized mothers who gave birth in our hospital. The prevalence of rectovaginal colonization among Slovak pregnant women is higher than 11.5 %, and probably ranges from 15 to 40 %[14]. Timing (35 to 37 weeks' gestation) of prenatal screening cultures is important. It is also important to collect both rectal and vaginal swabs. If only vaginal cultures are performed, 35 % of GBS colonized pregnant women remains unidentified[21]. According to current guidelines, IAP is considered to be sufficient only if its duration is at least 4 hours. However, the transmission of GBS to neonates exposed to less than 4 hours of intrapartum prophylaxis and their subsequent management require further study[22]. In our study group, 88 (35.2 %) newborns were exposed to less than 4 hours of IAP. Also, it seems that improvement of compliance with IAP is an important clinical issue. The compliance with IAP for women who delivered vaginally has been reported to be 93.8 %, and 53.2 % for women who delivered by caesarean section in the USA in 2000[23]. We identified four problems in the management of GBS colonized pregnant women. These problems complicate the evaluation of newborn's risk for EOGBSD and our decisions in neonatal management and care. Firstly, we lack information about prenatal screening culture results. Secondly, we lack information on the rectal culture and therefore we rely only on the vaginal culture result in the assessment of the mother's GBS status. Thirdly, compliance with IAP is not ideal, not every woman who qualified for IAP received it before delivery. Fourthly, the fact that the mother received IAP before delivery does not mean that its duration was satisfactory (at least 4 hours).

Attention should now be directed to preventing further cases of neonatal EOGBSD. Observational studies have suggested that the administration of intramuscular penicillin to the newborn immediately following delivery (within four hours after birth) may be an effective and safe method for preventing morbidity and mortality from EOGBSD. A significantly lower incidence of EOGBSD in the penicillin groups was reported, and there were no hypersensitivity reactions observed. However, a Cochrane review focused on a large randomized controlled trial[24] does not support the routine use of intramuscular penicillin to prevent EOGBSD in newborn infants[14]. In summary, the evidence from uncontrolled, retrospective and non-randomized controlled prospective studies supports the use of postnatal intramuscular penicillin in newborns to prevent EOGBSD[14,25,26,27]. We do accept that routine administration of antibiotics for all newborns born to mothers who received IAP to prevent GBS disease is not recommended[5,13]. There are three concerns which underlie the need to limit the target neonatal population for chemoprophylaxis: the potential for serious adverse reactions to penicillin, the possible emergence of antibiotic-resistant bacteria, and cost [1]. Therefore, we prefer postnatal chemoprophylaxis in a defined group of newborns at risk for the disease, using the strict indication criteria we have defined. Although the influence of IAP on the risk for GBS sepsis is well-defined, it is not known how much PAP reduces the risk for the EOGBSD.

PAP was administered in 15.6 % of the newborns born to GBS colonized mothers. According to our criteria, PAP was administered in 20 infants, although their mothers received antibiotic prophylaxis and the infants were at risk for GBS sepsis 0.18 / 1000. We keep in mind that IAP does not prevent all EOGBSD cases[5]. Postnatal prophylaxis may prevent other EOGBSD cases. Although PAP had to be prolonged in 8 newborns, these babies showed no clinical or laboratory signs of infection and we avoided empirical antibiotic therapy using ampicillin and gentamicin. According to the amniotic water culture results and the ear culture results in newborns, we can conclude that higher risk of GBS sepsis is associated with higher

incidence of positive microbiological testings. However, we admit that culture can be negative in a child with GBS if the mother received sufficient IAP[20].

Immunoprophylaxis seems to be the most promising method for the prevention of neonatal GBS infection in the future. There are various serotypes of GBS prevalent in different parts of the world. GBS antigens are being identified to overcome serotype-specificity and form the basis of a globally effective vaccine against this opportunistic pathogen[28]. GBS vaccines targeting the most virulent neonatal disease serotypes are currently under development. This would overcome growing concerns about the adverse effects of antibiotic prophylaxis, and about the development of antibiotic resistance[29]. At present, there is still no vaccine available for clinical use.

Because of no case of clinically manifested GBS infection and no case of definite GBS sepsis in this preliminary study, our strategy of management was considered to be effective in preventing EOGBSD in infants born to GBS colonized mothers. At this time, it seems to us that the strategy of selective PAP is an effective and safe method for reducing morbidity and mortality from early-onset GBS infections. We recommend a combination of intrapartum chemoprophylaxis and selective postnatal penicillin prophylaxis.

LIST OF ABBREVIATIONS

GBS – group B Streptococcus
EOGBSD – early-onset group B Streptococcal disease
IAP – intrapartum antibiotic prophylaxis
PAP – postnatal antibiotic prophylaxis

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