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Early-Onset Neonatal Sepsis: Group B Streptococcal Compared to *E. coli* Disease

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Abstract

Background: Early onset sepsis (EOS) of the newborn is a severe disease and associated with high morbidity and mortality. Aim of the study was to compare perinatal, short-term outcome and laboratory data of neonates with early-onset sepsis (EOS) either due to *Group B Streptococci* (GBS) or *Escherichia coli* (*E. coli*) infection.

Methods: Retrospective cohort analysis of all neonates with culture proven GBS and *E. coli* EOS born between 1993 and 2011 and hospitalized at the NICU of the Medical University of Graz, Austria. Data were analyzed regarding perinatal, laboratory and short-term outcome data.

Results: During the study period 100 neonates with EOS due to GBS and 11 neonates with *E. coli* infection were hospitalized at our NICU. Perinatal and short-term outcome data differed between GBS and *E. coli* infection regarding gestational age (median 38 vs. 32 weeks, p=.005), birth weight (median 3095 vs. 1836 grams, p=.031), presence of hypothermia (0 vs. 18%, p=.009), duration of mechanical ventilation (4 vs. 8 days, p=.019), duration of therapy with supplemental oxygen (9 vs. 2 days, p=.031), length of hospitalization (15 vs. 22 days, p=.039), presence of chorioamnionitis (17 vs. 46%, p=.041) and maternal fever (2 vs. 18%, p=.049). Mortality rates did not differ significantly (6 vs. 18%, p=.180). Laboratory data regarding white blood cell count, IT-ratio, and CRP value were not different between groups within the first 72 hours of life. There was a significant decrease of GBS sepsis during the study period (p=0,014).

Conclusion: Main differences between GBS and *E. coli* infections were due to higher rates of preterm birth in the *E. coli* group, clinical and laboratory characteristics only differed marginally.

Keywords: Early-onset sepsis; *Escherichia coli*; Group B streptococcus; Neonate; Preterm infant

Introduction

Early onset sepsis (EOS) of the newborn is a severe disease and associated with high morbidity and mortality. At present *Group B Streptococci* (GBS) and *Escherichia coli (E. coli)* are the most common pathogens in developing countries, most infants with GBS are born at term, infants with *E. coli* are more common born preterm [1,2]. After the implementation of preventing strategies based on administration of intrapartum antibiotic prophylaxis the incidence of GBS decreased over the last 15 years 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 the last years [3]. In 1996 CDC recommended either a risk-based approach for intrapartum administration of antibiotics or an universal screening for vaginal or rectal GBS colonization for all pregnant woman between 35 and 37 weeks of gestation. In the revised guidelines of 2002 CDC only recommended the universal screening. In Austria there is still a risk-based approach and no universal GBS screening [4,5]. There are concerns that the widespread use of antibiotics could increase the frequencies of non-GBS or antimicrobial-resistant pathogens [6-9].

Aim of the study was to compare perinatal data, morbidities, mortality, therapies and laboratory data of neonates with EOS either due to GBS or *E. coli* infection.

Methods

Study design

This was a retrospective study at the NICU of the Pediatric Department of the Medical University of Graz. Data were collected between 1993 and 2011. Inclusion criteria were a culture proven sepsis caused by GBS or *E. coli* diagnosed within the first 72 hours of life. Exclusion criteria were missing or incomplete data, a culture-negative clinical sepsis and an unknown state of infection.

Analyzed neonatal variables included sex, gestational age (GA), birth weight (BW), preterm birth, Apgar scores at 1,5 and 10 minutes, clinical signs (tachycardia, bradycardia, tachypnea, apnea, hypotension, hypothermia, fever), therapy (mechanical ventilation (CPAP included), duration of mechanical ventilation, high frequency oscillation, surfactant, nitrogen oxide, immunoglobulin, catecholamine), morbidities (respiratory distress syndrome, pneumonia, pneumothorax, persistent pulmonary hypertension of the newborn, seizures, periventricular leukomalacia, intra-/periventricular

hemorrhage, hypoxic ischemic encephalopathy, septic shock, multi-organ failure, disseminated intravascular coagulation, renal failure, mortality) length of hospitalization and laboratory parameters (C-reactive protein - CRP, white blood cell count, IT-ratio) on the 1st, 2nd and 3rd day of life. Maternal variables included prolonged rupture of membranes (PROM >18 hours), preterm premature rupture of the membranes (PPROM), presence of chorioamnionitis and maternal fever.

Definition of EOS

EOS was defined as culture proven sepsis (a positive blood or cerebrospinal fluid culture) within the first 72 hours of life.

In addition to a positive blood or cerebrospinal fluid culture they had to meet the following criteria: clinical signs of sepsis in ≥ 1 with either ≥ 1 maternal risk factor or ≥ 1 abnormal laboratory marker.

Clinical signs of sepsis included: respiratory symptoms (apnea, tachypnea (>60/min), retractions, cyanosis, and respiratory distress), cardiocirculatory symptoms (tachycardia (>180/min) or bradycardia (<100/min), arterial hypotension) neurological symptoms (irritability, lethargy, and seizures), poor skin color or prolonged capillary refilling time (more than 2 seconds), fever or hypothermia (core temperature >38°C or <36°C).

Maternal risk factors included: PROM (more than 18 hours) or PPROM, clinical chorioamnionitis (uterine tenderness or foul-smelling amniotic fluid, maternal leucocytosis >12,000/µL, and maternal or fetal tachycardia) and maternal fever >38°C during labor. Laboratory sepsis marker were white blood cell (WBC) count >34,000/µL or <9000/µL, absolute neutrophil count >14,400/µL or <7,000/µL (<2,000/µL during the first 24 h of life), CRP >8 mg/L, immature-to-total neutrophil ratio (IT ratio) >0.2 [10-12].

Variable	GBS cases (n=100)	*E. coli* cases (n=11)	P value
male	57 (57)	6 (54.5)	n s
gestational age (weeks)[1]	38	32	0.005
birth weight (g)[1]	3095	1836	0.031
APGAR 1[1]	8	7.5	n s
APGAR 5[1]	9	8	0,025
APGAR 10[1]	10	8	0,024
Risk factors			
preterm	42 (42)	8 (72.7)	n.s
Rupture of membranes >18 h	32 (32)	5 (45.5)	n.s
chorioamnionitis	17 (17)	5 (45.5)	0.041
maternal fever >38°C	2 (2)	2 (18.2)	0.049

data are given as n(%). n s= not significant.

[1]data are given as median

Table 1: Perinatal data of study population.

Statistical analysis

Statistical analyses were performed with SPSS version 20 (SPSS, Chicago, IL, USA). Descriptive statistics were obtained for all categorical variables. Statistical significance was determined for unadjusted comparisons by Mann-Whitney-U-test for continuous variables and by Fisher´s exact test for categorical variables. A univariate analysis was performed and the significance level was set at $p<.05$. The Pearson correlation coefficient was used to analyze the association between the frequency of occurrence of pathogens and the time.

Results

During the study period 100 neonates with EOS due to GBS and 11 neonates with *E. coli* infection were hospitalized at our NICU.

Forty-two percent of the infants with GBS and 73 percent with *E. coli* EOS were born preterm. Thirteen percent of the infants with GBS and 36 percent with *E. coli* infection had a very-low-birth-weight (VLBW, < 1500 grams)). GBS was the most common pathogen among term (95%), preterm (84%) and VLBW (76%) infants.

There was a significant reduction of GBS during the study period ($p=.0.014$). The Pearson correlation coefficient was -0.601.

In comparison to neonates with GBS sepsis, neonates with *E. coli* sepsis had a lower GA and a lower BW. The risk factors chorioamnionitis and maternal fever occurred more frequently in the *E. coli* group. Perinatal data are shown in Table 1.

Clinical signs, therapy, morbidities and the length of hospitalization are shown in Table 2. There were significant differences regarding hypothermia, duration of mechanical ventilation and length of hospitalization.

Laboratory data not differed between groups (Table 3).

Discussion

In spite of the implementation of preventing strategies, GBS remained the leading cause of EOS among term, preterm and VLBW infants in our study. There was a significant decrease of GBS sepsis over the study period, but no increase of EOS caused by *E. coli* neither among term nor preterm or VLBW infants like in other studies [13,14]. Intrapartum antibiotic treatment is suggested to cause negative blood cultures and thus, maybe some infants with culture proven EOS were not identified.

Stoll et al. [1] reported that neonates with GBS sepsis were mostly born at term, and those with *E. coli* sepsis preterm. In their study the risk factors chorioamnionitis and premature rupture of membranes occurred more frequently among infants with *E. coli* sepsis compared to infants with GBS sepsis. Also mortality rates were higher among infants with *E. coli* EOS, but differences were not significant anymore after adjustment for GA. Mayor-Lynn et al. [15] reported that *E. coli* sepsis cases had a lower birth weight, a higher percentage with 5-minute Apgar score <7, and a longer stay in the hospital neonatal intensive care unit and required mechanical ventilation more frequently. Death after early-onset neonatal sepsis with *E. coli* was also more frequent. Additionally the risk factor chorioamnionitis was more frequently found among neonates with GBS sepsis. The authors concluded that EOS with *E. coli* was associated with more morbidity and a higher mortality rate compared with early-onset GBS disease.

	Variable	GBS cases (n=100)	*E. coli* cases (n=11)	P value
Clinical signs	tachykardia	12 (14.5)	1 (11,1)	n.s
	bradykardia	2 (2,4)	1 (11,1)	n.s
	tachypnea	44 (72.1)	5 (83.3)	n.s
	apnea	21 (21)	3 (27.3)	n.s
	hypotension	39 (39)	6 (54.5)	n.s
	hypothermia	0 (0)	2 (18.2)	0.009
	fever	14 (14)	0	n.s
Therapy	mechanical ventilation (CRAP itcluded)	66 (66.7)	10 (90.9)	n.s
	duration of mechanical venttahon (d)[1,2]	4	8	0.019
	duration of therapy with supplemental oxygen(d)[1,2]	2	9	0.031
	high frequency oscillation	7(7.1)	2(18.2)	n.s
	surfactant	38 (38.8)	8 (72.7)	n.s
	nitrogen oxide	8 (8.2)	0 (0)	n.s
	itninunoglobuitn	19 (19.2)	2 (18.2)	n.s
	catecholarrine	39 (39)	6(54.5)	n.s
Morbidities	respiratory distress syndrome	26 (26)	6(54.5)	n.s
	pneumonia	11 (11)	0 (0)	n.s
	pneurnothorax	5 (5)	0 (0)	n.s
	persistent pulmonary hypertension ofthe newborn	9(9)	1 (9.1)	n.s
	seizures	4 (4)	0 (0)	n.s
	periventrioular leukomalacia	1 (1)	0 (0)	n.s
	intra-iperiventriculsr hemorrhage	13(13)	4 (36,4)	n.s
	hypo= & cheerio encephalopathy	3 (3)	1 (9.1)	n.s
	septic shock	3 (3)	2 (18.2)	n.s
	multi organ failure	1 (1)	0 (0)	n.s
	disseminated ntravascutar coagulation	2 (2)	0 (0)	n.s
	renal failure	5 (5)	1 (9.1)	n.s
	mortality	6 (6)	2 (18.2)	n.s
Length of hospitalization (d) [1,2]		15	22	0.039
data are given as n (%), n.s= not significant. [1]data are given as median; [2]neonates who died within 3 days were excluded				

Table 2: Clinical signs, therapy, morbidities, length of hospitalization of GBS and *E. coli* cases.

Our results were comparable to those reported by Stoll et al. [1] and Mayor-Lynn et al. [15]. Most infants with GBS sepsis were born at term and those with *E. coli* sepsis preterm. In comparison to neonates with GBS sepsis, neonates with *E. coli* sepsis had a lower BW, a lower GA and a longer stay at the neonatal ward. The Apgar scores at 5 and 10 minutes were lower. Mortality rate did not differed significantly between the two groups. The risk factor chorioamnionitis and maternal fever occurred more frequently in the *E. coli* group. We found no difference regarding the frequency of mechanical ventilation between the two groups, but neonates with *E. coli* sepsis had a longer duration of ventilation and longer therapy with supplemental oxygen. The higher rate of hypothermia in the *E. coli* group might be the result of the higher rate of preterm birth, as far as preterm infants are known

to more likely react with hypothermia to a bacterial infection than term infants [16].

Limitations of this study include the relatively small study population and the long study time period, the retrospective design of the study even when data were collected carefully and the missing control group of uninfected neonates – the latter was not the aim of our study. Nevertheless our results are proven by larger studies in the field [1,15]. The long study time period enabled to demonstrate a global reduction in GBS disease. This might be the positive result of the risk-factor based GBS screening in Austria with subsequent intrapartum antibiotics therapy.

	Variable	GBS cases (n=100)	*E. coli* cases (n=11)	P value
CRP (mg/l)	1st day	25	50.2	n.s
	2nd day	29	17.5	n.s
	3 rd day	22.6	12.85	n.s
White blood cell count (µL)	1st day	13800	2400	n.s
	2nd day	17400	17250	n.s
	3 rd day	15190	14200	n.s
IT-Ratio	1st day	0.23	0.37	n.s
	2nd day	0.24	0.21	n.s
	3 rd day	0.325	0.145	n.s
data are given as median, n.s= not significant				

Table 3: Laboratory parameters of GBS and *E. coli* cases.

Preventive strategies for *E. coli* sepsis might be based on risk factor analysis that identified chorioamnionitis and maternal fever occurring significantly more frequent in cases of *E. coli* infection. Despite a reduction of cases with GBS EOS over the study period vaccines for the prevention of GBS disease are urgently warranted and might further contribute to a reduction on the burden of GBS disease [17,18].

In conclusion our study confirmed that the main differences between GBS and *E. coli* sepsis were attributable to higher rates of preterm birth in the *E. coli* group. Laboratory data were not helpful in the differentiation of both pathogens.

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