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ORIGINAL ARTICLES AND REVIEWS

Characteristics of neonatal GBS disease during a multicentre study (2007-2010) and in the year 2012

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Abstract

Introduction. The characteristics of Group B Streptococcal (GBS) early onset (EOD) and late onset (LOD) neonatal infections in Italy were analyzed. Two periods were considered, a first 3-years period (2007-2010), when notification of GBS infections was enforced under the auspices of the Italian Ministry of Health, and a second 1 year period (2012) when reporting on neonatal GBS disease continued on voluntary basis.

Methods. A standardized form was used to collect data on cases of neonatal GBS disease. They included both maternal and neonatal data.

Results and discussion. The two surveys underlined that preterm deliveries, precipitous labor and negatively GBS screened mothers are common causes of EOD occurrence, possibly explained by inadequate, or lack of, intrapartum antibiotic prophylaxis. Nevertheless, measures for reducing prevention failures and EOD incidence by an higher adherence to prevention strategies, as the Centre for Disease Control recommendations, are still possible and should be encouraged.

Key words

- surveillance
- group *B Streptococcus*
- early-onset disease
- late-onset disease
- intrapartum antibiotic prophylaxis

INTRODUCTION

Streptococcus agalactiae (Group *B Streptococcus,* GBS) is a commensal of the human intestinal and genito-urinary tract. As a pathogen, GBS emerged in the 1970s as the leading cause of invasive perinatal infections in developed countries [1].

Invasive GBS infections can present either with an early onset disease (EOD) that occurs generally within 12 hours as respiratory distress, apnea, leading to sepsis and/or pneumonia or with a late onset disease (LOD) occurring between one week and three months of life and accounting for most meningitis cases and deaths [2, 3].

Up to 30% of pregnant women can be asymptomatically colonized with GBS in the vagina and/or rectum and represent the primary risk factor for the vertical transmission during labor. In the absence of any prevention strategies, about 50% of neonates born to GBS colonized mothers are colonized at the mucosal and skin sites and an estimated 1-2% develop early-onset GBS invasive infections [4, 5].

Prevention strategies consider an intrapartum antibiotic prophylaxis (IAP) by the intravenous administration of penicillin/ampicillin (or clindamycin in the case of serious penicillin allergy) to parturient women in all cases that increase the risk for EOD. Guidelines recommend the use of one of two approaches to identifying women who should receive intrapartum antibiotic prophylaxis: a risk-based approach or a culture-based screening approach. The risk-based method identifies candidates for intrapartum chemoprophylaxis according to the presence of any of the following intrapartum risk factors: delivery at < 37 weeks' gestation, intrapartum temperature ≥ 38.0 °C or rupture of membranes for ≥ 18 hours. The culture-based screening method consists in the screening of all pregnant women for vaginal and rectal GBS colonization between 35 and 37 week's gestation. Colonized women are offered intrapartum antibiotics at the time of labor onset or rupture of membranes if before labor [6-8].

In US, EOD has declined by 70% since increased use of intrapartum antibiotic prophylaxis has occurred in the early 1990s; nevertheless, this approach has had only a slight effect in the reduction of LOD. Since 2002, the US Centre for Diseases Control (CDC) recommendations for the prevention of the newborn invasive GBS disease opted for the universal prenatal culture-based screening approach [9].

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In Europe, routine bacteriological screening of all pregnant women for antenatal GBS carriage to optimize the identification of women who should receive IAP is recommended as part of national guidelines in Spain (1998), France (2001), Belgium (2003), Germany (1996), Czech Republic (2008), Poland (2008), Switzerland (2007) but not in UK, Holland and Norway that opted for the risk-based approach [10-13].

Under both strategies, intrapartum antibiotic prophylaxis is recommended for women with GBS bacteriuria at any time during their current pregnancy or for women who had given birth previously to an infant with invasive early onset GBS disease. Intrapartum antibiotic prophylaxis is not indicated, if a cesarean delivery is performed before onset of labor on a woman with intact amniotic membranes, regardless of GBS colonization status or gestational age [9].

In Italy neither guidelines for the prevention of group *B Streptococcus* invasive neonatal infections nor an active surveillance system for the notification of disease exist. In November 2010 the recommendation for GBS antenatal screening (vaginal-rectal swab at 36-37 weeks of gestation) and IAP for carriers has been included in a guideline promoted by the Italian Ministry of Health regarding routine controls schedule in pregnancy [14]. The test is on payment because, despite the recommendation, it is not included in the list of the national health services freely provided to pregnant women [15-18].

Only an Italian Region, Emilia-Romagna (ER), located in the northern part of Italy, has set up a local GBS Working Group since 2003, promoting common prevention strategies according to the CDC recommendations for an universal screening-based approach. This group has produced valuable data on the incidence of GBS disease and clinical features of early and late onset GBS disease in ER [19-25].

A multicentre study, funded by the Italian Ministry of Health and coordinated by the Italian National Institute of Health (Istituto Superiore di Sanità, ISS) on the invasive neonatal GBS infections was pursued in the years 2007-2010 [17]. After that, the reporting on neonatal GBS disease to ISS continues on voluntary basis.

This paper compares the clinical characteristics of neonatal GBS cases collected both during the multicentre study and the year 2012.

METHODS

A standardized form, inspired to that adopted in ER, was used to collect data on cases of neonatal GBS disease. They included both maternal data (antenatal colonization, gestational age, ethnicity, mode of delivery, risk factors, antibiotic administration) and neonatal data (sex, ethnicity, onset of symptoms, clinical manifestation, outcome, hospital stay duration, site of GBS isolation). The operational protocol adopted during the 2007-2010 multicentre study identified as GBS neonatal infections only culture proven cases where GBS was isolated from a normally sterile body site such as blood or cerebrospinal fluid (CSF) in infants aged ≤ 90 days, while also cases of clinical sepsis (where GBS was isolated from broncoalveolar lavage or gastric aspirate) were accepted during the surveillance in the year 2012.

The GBS Working Group of Emilia-Romagna and nine hospitals located in different part of Italy, covering about one tenth of national annual births, participated to the 2007-2010 multicentre study while the year 2012 surveillance relied on the notification by any national hospital on voluntary basis.

In both surveillance periods, all participating birth centres reported to follow CDC recommendations.

RESULTS AND DISCUSSION

In the years 2007-2010 a total of 89 cases were received, of which 75.3% from the ER. In the year 2012, a total of 50 GBS neonatal infection notifications were received; in particular, 19 cases were from the GBS Working Group of Emilia-Romagna (38%) and the remaining cases from fourteen hospitals located in nine Italian Regions. These represent encouraging data, reflecting both the lowering of the incidence of GBS perinatal disease in ER due to the constant improvement in the adherence to the prevention protocols (in 2012, the incidence of the perinatal GBS disease was 0.17 cases/1000 live births) and the higher participation and collaboration in the GBS cases notification by other national birth centres.

Table 1 summarizes the data collected on GBS neonatal infections in the years 2007-2010 compared to those collected in the year 2012. An interesting aspect in both the surveillance periods was the high proportion of infections among preterm infants (27% in the first period and 22.5% in the second period). This finding could be explained by different considerations: often IAP preventing the transmission of the infection by mother to neonate in the case of maternal GBS colonization could not be efficiently administrated in the case of precipitous labor characterizing most of preterm deliveries; on the other side, the improved clinical management of very prematures neonates reduced the incidence of septic abortion cases. The percentage of mothers of these babies that received antenatal screening for GBS (72% and 80% in the two surveillances, respectively, *Table 1*) was lower than those of full-term babies (usually 90-to-95%), because deliveries mostly occurred before the recommended gestational age for the antenatal screening [17, 24].

The most frequent clinical manifestation of neonatal GBS infection was sepsis, followed by bacteremia and meningitis. About 2% of mortality was registered in both surveillances. The hospital stay duration (surveyed only in the year 2012) was significantly higher in the case of preterm patients than in term infants affected by EOD, while no difference in the hospital stay length between pre-term and full-term patients was observed in the case of LOD (16-20 days).

About 35-40% of EOD were from negative screened mothers in both surveillance periods *(Table 1* and *Table 2)*. This finding has been elsewhere reported [17, 22, 24, 26, 27] and it constitutes, nowadays, the prominent failure in the prevention strategies. As pointed out above, approximately 10%-30% of pregnant women are colonized with GBS in the vagina or rectum. The gastrointestinal tract serves as the primary reservoir for GBS and is the likely source of vaginal colonization.

Table 1
Data collected on Group B Streptococcal (GBS) neonatal infections during the surveillance periods

	2007-2010	2012
Early onset disease (0-7 days)	45 cases	29 cases
Late onset disease (8-90 days)	44 cases	21 cases
Female/male ratio	1.12	0.75
Ethnical group		
White European	89.4%	84.0%
Black African	11.2%	4.0%
Asian	3.4%	8.0%
Mixed	--	2.0%
Not reported	10.1%	
Prematurity (< 37 wks)	27%	22.5%
Bacterial isolation		
Blood	78.6%	64.0%
Cerebrospinal fluid	6.8%	4.0%
Blood plus cerebrospinal fluid	10.1%	18.0%
Molecular identification test	4.5%	--
Not sterile sites	--	14.0%
Clinical manifestation		
Sepsis	48.3%	42.0%
Bacteraemia	13.5%	18.0%
Meningitis	12.3%	6.0%
Sepsis plus meningitis	4.5%	20.0%
Septic shock	4.5%	--
Septic arthritis	2.3%	--
Cellulitis	1.1%	--
Not reported	13.5%	--
Clinical sepsis	--	14.0%
Outcome		
Total recovery	62.9%	82.0%
Altered neuroimages	2.2%	--
Permanent neurological sequelae	7.8%	8.0%
Mortality	2.2%	2.0%
Not reported	24.7%	8.0%
Hospital stay (average of days)		
Early onset disease (preterm)	--	145 days
Early onset disease (term)	--	20 days
Late onset disease (preterm)	--	20 days
Late onset disease (term)	--	16 days
Maternal antenatal GBS screening	72.0%	80%
Positive	31.5%	32%
Negative	40.4%	48%
Negative mothers in early onset disease	42.2%	34.5%
Negative mothers on late onset disease	38.6%	52.4%

Because GBS colonization status can change over the course of a pregnancy, the timing of specimen collection as well as the laboratory method used for specimen processing are very important. GBS cultures performed until less than 5 weeks before delivery are considered reliable [9]; nevertheless, the positive predictive value of prenatal cultures for GBS carriage during labor varies through the literature and may sometime be lower [28, 29].

Regardless of the microbiological test selected to identify GBS, the use of a selective enrichment broth improves detection substantially. When direct agar plating is used instead of selective enrichment broth, only heavy colonization is detected and as many as 50% of women who are GBS carriers have false-negative culture results [9, 30].

The recommended combined rectal-vaginal swabbing increased sensitivity, but the relevant proportion of perinatal infections from negative mothers strongly suggests the real adherence to the specimen processing protocol should be evaluated and new solutions should be proposed. Rapid molecular diagnostic assays to be used at the time of delivery are being developed and could contribute to identify carrier women at labor to administrate IAP in a more proper way [9, 28].

In the case of LOD, up to 50% of mothers resulted negative to the antenatal screening, confirming an horizontal transmission as the cause of GBS infection and the relatively inefficiency of IAP in LOD prevention *(Table 2)*.

Table 2 reports the prevention strategies adopted at labor during the two surveillance periods, depending on the evaluation of maternal colonization status and presence of risk factors, only for those cases that subsequently developed perinatal GBS infections. In case of antenatal positive screening, only 60% and 27.3% of women whose babies developed EOD received IAP in the two surveillance periods, respectively. In all cases but one the IAP was administered for less of the 4 hours recommendation [9]. Precipitous delivery, often because of prematurity, was the main reason for an inadequate IAP. These observation is supported by other investigations where for as many as 45-50% of women is not possible to meet the 4 hours recommendation because of the rapidity of their labors [29; 31-34].

Other less frequent missed opportunities for prevention included an inadequate route of antibiotic administration, the use of macrolides to which the GBS resulted resistant, home delivery [17, 24].

When the antenatal screening was not performed and the evaluation of risk factors only at labor was done, the EOD cases were either from eligible mothers who didn't receive IAP or received inadequate IAP (45.4% and 71.4%).

Deviations to the CDC guidelines adherence was noted in the case of antenatal negative screening. Regardless of intrapartum risk factors, CDC guidelines do not recommend IAP if parturients are not GBS colonized. This approach is not always followed by national birth centres, most of which prefer to administrate IAP in this situation [17]. Also in this case, however, IAP failure and development of EOD occurred in 26.3%

Table 2
Prevention strategies adopted in labor during the two surveillance periods in those cases which developed early onset disease and late onset disease

		Antenatal screening (positive)	Antenatal screening (negative)	Antenatal screening (not done)
2007-2010	**Early onset disease**	15	19	11
	Risk factors	9	9	6
	IAP > 4 hrs	0	0	0
	IAP < 4hrs	9*	5	3**
	CDC guidelines adherence	60%	NA§	45.4%
	Late onset disease	13	17	14
	Risk factors	2	5	9
	IAP > 4 hrs	0	0	1
	IAP < 4 hrs	10	4	3
	CDC guidelines adherence	77%	NA§	28.6%
2012	**Early onset disease**	11	11	7
	Risk factors	6	3	3
	IAP > 4 hrs	1	1	0
	IAP < 4 hrs	2	2	1
	CDC guidelines adherence	27.3%	NA§	71.4%
	Late onset disease	5	13	3
	Risk factors	2	0	3
	IAP > 4 hrs	1	0	1
	IAP < 4 hrs	4	0	1
	CDC guidelines adherence	100%	100%	66.6%

* In one case the route of administration was inadequate (oral) and in one case a not suitable antibiotic was administrated; ** in two cases the route of administration was inadequate (oral); § not applicable, because IAP was administered despite CDC recommendations.

and 27.2% respectively. The higher proportion of IAP failure because of the inadequate time of administration (deliveries with fewer than 4 hours of antibiotics) in the case of positive antenatal screening respect to when the antenatal screening was negative or not done, underlines that, among all risk factors responsible for the vertical bacterial transmission, the heavy maternal colonization remains the prominent cause for developing EOD [35].

In case of LOD, the relevant proportion of mothers who had received IAP (77% and 100% in the two surveillance periods, respectively) confirmed its inefficacy in disease prevention and the importance of a better understanding of the bacterial transmission mode responsible for the onset of this perinatal infection. This observation is also confirmed by the microbiological characteristics of GBS bacterial strains responsible for EOD and LOD. The serotype distribution of GBS strains isolated both from EOD and vagino-rectal antenatal screening is very similar, confirming that the vertical transmission from mother to baby is the principle cause of disease; on the other hand, more than 87% of LOD cases is caused by a particular clone, worldwide diffused [17, 36].

CONCLUSIONS

Preterm deliveries, precipitous labor and negative screened mothers are the prominent causes for an inadequate or lack of IAP and EOD occurrence. Nevertheless, measures for reducing prevention failures and EOD incidence by an higher adherence to the CDC recommendations are still possible and encouraged. A vaccine, currently under study [37, 38], to prevent group B Streptococcal disease could contribute to prevent both EOD and LOD, the route of bacterial transmission of the latter being poorly understood and for which CDC recommendations are ineffective.

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Conflict of interest statement

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