The Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) study of neonatal group B streptococcal infections in Canada

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OBJECTIVES: To determine the presentation and medical outcomes of neonatal group B streptococcus (GBS) disease in Canada, and describe maternal and obstetrical risk factors.
DESIGN: Retrospective review of health records and laboratory databases using standardized data collection forms.
SETTING: All neonates diagnosed with GBS infections in 1992 at 13 Canadian paediatric centres.
RESULTS: A total of 105 infants meeting the criteria for neonatal GBS disease were identified. The majority of cases (78 or 74.3%) had early-onset disease (EOD); 78.9% (60 of 76) of these cases presented within 24 h of delivery. Rates of EOD (less than seven days) varied from 0.44/1000 live births to 2.1/1000 live births, with an overall rate of 1.2/1000 live births. Pneumonia was the most common clinical illness (43.8%), followed by bacteremia without focus (23.8%) and meningitis (16.2%). At least one maternal risk factor for neonatal GBS disease was noted in 46 of 78 (59%) infants with EOD. A median of one dose (range one to 23 doses) of intrapartum antibiotics was given in 18 of 75 (24%) of the pregnancies. Overall, the mean gestational age at birth was 36.2±4.7 weeks, with 38 of 96 (39.6%) infants having a gestational age at birth younger than 37 weeks (31 of 73 [42.5%] EOD cases were born with a gestational age younger than 37 weeks). The median birth weight was 3099 g (range 610 g to 4830 g). Thirty of 94 (31.9%) infants had a birth weight less than 2500 g. Seventeen (16.2%) infants died.
CONCLUSIONS: In 1992, neonatal GBS disease was a significant cause of morbidity and mortality in Canadian infants. More than half of the cases identified in this study could have been potentially preventable by the use of intrapartum antibiotics for women with known risk factors. There is a need for prospective studies to better define risk factors and preventative measures for neonatal GBS infections in Canada.

Key Words: *Group B streptococcus; Neonatal; Outcome*

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L'étude du réseau coopératif d'investigateurs pédiatriques sur les infections au Canada (PICNIC) traitant des infections streptococciques de groupe B au Canada.

OBJECTIFS : Établir la présentation et les issues médicales de la maladie streptococcique de groupe B (SGB) néonatale au Canada et en décrire les facteurs de risque maternels et obstétriques.

MÉTHODOLOGIE : Étude rétrospective des dossiers médicaux et banques de données de laboratoire au moyen de formulaires de collecte de données normalisés.

EMPLACEMENT : Tous les nouveau-nés ayant reçu un diagnostic d'infection SGB dans 13 centres pédiatriques canadiens en 1992.

RÉSULTATS : Au total, on a repéré 105 nourrissons respectant les critères de maladie SGB néonatale. La majorité des cas (78, ou 74,3 %) avaient souffert d'une maladie à apparition précoce (MAP); 78,9 % (60 sur 76) de ces cas se manifestaient dans les 24 heures suivant l'accouchement. Le taux de MAP (moins de sept jours) oscillait entre 0,44/1 000 naissances vivantes et 2,1/1 000 naissances vivantes, la moyenne globale s'établissant à 1,2/1 000 naissances vivantes. La pneumonie constituait la maladie clinique la plus courante (43,8 %), suivie de la bactériémie sans foyer (23,8 %) et de la méningite (16,2 %). On a remarqué au moins un facteur de risque maternel de maladie SGB néonatale chez 46 des 78 (59 %) nourrissons atteints de la MAP. Une dose médiane (écart de une à 23 doses) d'antibiotiques intrapartum a été administrée dans 18 des 75 (24 %) grossesses. Dans l'ensemble, l'âge gestationnel moyen à la naissance était de 36,2 ± 4,7 semaines, et 38 des 96 (39,6 %) nourrissons avaient moins de 37 semaines d'âge gestationnel à la naissance (31 sur 73 [42,5 %] des cas de MAP avaient moins de 37 semaines d'âge gestationnel). Le poids moyen à la naissance s'élevait à 3 099 g (écart de 610 g à 4 830 g). Trente des 94 (31,9 %) nourrissons pesaient moins de 2 500 g à la naissance. Dix-sept (16,2 %) nourrissons sont décédés.

CONCLUSIONS : En 1992, la maladie SGB néonatale représentait une cause importante de morbidité et de mortalité chez les nourrissons canadiens. Plus de la moitié des cas repérés dans le cadre de cette étude aurait peut-être pu être évitée grâce à l'administration d'antibiotiques intrapartum aux femmes présentant des facteurs de risque connus. Il faudra procéder à des études prospectives pour mieux définir les facteurs de risque et les mesures préventives d'infection SGB néonatale au Canada.

Group B streptococcus (GBS) (*Streptococcus agalactiae*) has been recognized as a significant cause of perinatal morbidity and mortality for more than two decades. GBS is the most significant cause of bacterial sepsis and meningitis among newborn infants (1). The primary source of infection in the neonate is the colonized maternal birth canal, with transmission occurring before or during the birth process. Estimates of GBS colonization rates in pregnant women range from 12% to 35% (2-18). Forty per cent to 75% of infants born to colonized mothers are born colonized (18). Rates of neonatal infection range from 0.3 to 3/1000 live births (1,19-27). Two patterns of GBS infection occur in the newborn. Early-onset disease (EOD) (younger than seven days of age) is more common and has a higher rate of mortality of 6% to 20% (1,19-27). Late-onset disease (LOD) (seven days to three months of age) occurs less commonly, accounts for 20% to 30% of all neonatal GBS cases and has a lower associated mortality, estimated at 5% to 15% (18,28,29). A 1993 economic analysis estimated the cost per case of EOD at US$33,800, and the cost per case of LOD at US$83,070 (30). Numerous investigators have evaluated risk factors for GBS to establish predictors of perinatal disease. Although infant colonization is usually the direct result of maternal colonization (18), only 1% to 2% of women who are carriers deliver infants with invasive GBS disease. Thus, it is clear that maternal colonization is necessary, but is not the sole determinant of GBS disease in the newborn. There is evidence that risk factors vary geographically. An Australian study found that 80% of GBS-infected infants in Melbourne were born preterm; by contrast, population-based surveillance in Atlanta found that only 28% of affected infants were born prematurely (1,31). Because risk factors for invasive disease across Canada have not been identified, we conducted a retrospective study to identify maternal antecedents, clinical manifestations and outcomes of GBS disease in infants younger than three months.

MATERIALS AND METHODS

Setting

The Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) is a collaborative network of paediatric infectious disease specialists who conduct studies at 16 university-affiliated paediatric centres in Canada <cids.medical.org/picnic/home.html>. In this study, 13 sites serving as primary and tertiary care centres in urban areas across Canada participated.

Patient profile

Data were collected between 1995 and 1996 using a standardized data collection form. Information gathered included basic demographic data, perinatal and obstetrical history, bacteriological data, and data relating to the illness of infants and medical outcomes (ie, major and minor disabilities). Neonatal GBS infection was diagnosed by isolation of GBS from blood, cerebrospinal fluid or other normally sterile body sites in an infant younger than three months. GBS pneumonia was diagnosed when there was radiological evidence of infiltrates on chest radiogram, in addition to blood isolate of GBS.

The following case finding strategies were used.

1. The database at each participating centre's microbiology laboratory was searched to locate all positive blood and cerebrospinal fluid cultures meeting the case definition between January 1, 1992, and December 31, 1992. The year 1992 was selected in order to capture the patterns of neonatal GBS disease before widespread dissemination of the American Academy of Pediatrics neonatal GBS prevention guidelines (published in 1992) (32), and the Canadian Consensus Guidelines (published in 1994) (33).
2. Health records were used to identify patient charts coded with 12 different classifications

TABLE 1: Rates of neonatal group B streptococcal (GBS) disease identified at participating hospitals across Canada

Hospital code	Total number of GBS cases (number with EOD)	Number of cases eligible for rate calculation (number with EOD)*	Total number of live births	Total cases/1000 live births	EOD cases/1000 live births
1†	7 (7)	7 (7)	NA	NA	NA
2†	8 (2)	8 (2)	12,767	0.63‡	NA
3	5 (5)	2 (2)	3388	0.59	0.59
4	10 (6)	6 (6)	2880	2.1	2.1
5†	21 (17)	NA	0	NA	NA
6†	6 (3)	NA	0	NA	NA
7	13 (12)	8 (8)	7027	1.1	1.1
8	2 (2)	1 (1)	2263	0.44	0.44
9†	3 (1)	NA	0	NA	NA
10	3 (3)	3 (3)	5726	0.52	0.52
11	12 (10)	9 (7)	4877	1.8	1.4
12†	4 (2)	0	0	NA	NA
13	10 (7)	10 (7)	12,652	0.79	0.55

**Cases were only eligible for rate calculation (cases per 1000 live births) if they were born at the participating hospital or if the hospital involved was responsible for the care of all neonates in the region; †Paediatric hospitals with no delivery. Exact referral base uncertain; ‡Minimum estimate because some early-onset disease (EOD) cases may have been treated at maternity hospitals within the same region where they were delivered. Late-onset disease cases cared for in this hospital for the whole region; NA Not available.*

TABLE 2: Use of intrapartum antibiotics in mothers of infants with early-onset neonatal group B streptococcal (GBS) disease in the presence or absence of clinical risk factors

Clinical risk factor	Number (%) with risk factor receiving antibiotics*	Number (%) without risk factor receiving antibiotics*	P
Intrapartum fever >38°C	8/13 (61.5)	4/58 (6.9)	<0.001
Chorioamnionitis	6/10 (60)	5/53 (9.4)	<0.001
GBS positive status†	5/6 (83.3)	0/1 (0)	0.09
Prolonged rupture of membranes ≥12 h	9/30 (30)	5/37 (13.5)	0.10
Prolonged rupture of membranes ≥18 h	7/17 (41.2)	7/50 (14)	0.02
Gestational age <37 weeks	8/31 (25.8)	6/42 (14.3)	0.22

**Numerator is number of patients given antibiotics, denominator is number of patients with clinical risk factor present or absent. Denominators do not always total 76 because of missing data; †GBS positive or negative results either from screening before delivery or from cultures analyzed at delivery. Most women did not have this information recorded on their health record*

according to the International Statistical Classification of Diseases and Related Health Problems, 9th Revision, Clinical Modification (ICD9-CM) codes (041.02, 320.2, 320.89, 320.9, 320.82, 130.0, 770.0, 038.42, 038.0, 038.1, 038.8, 038.9) that may represent GBS infection related to hospital discharges during the same period.

Statistical analysis

The χ^2 test and Fisher Exact test (for expected cells less than five) were used to compare group proportions. The Mann-Whitney U test was used to compare medians, and the Student's *t*-test was used to compare means.

RESULTS

One hundred and five infants met the criteria for neonatal GBS disease. Seventy-eight of these (74.3%) had EOD. The overall rates of disease at hospitals where birth cohort denominators were available was 1.2/1000 deliveries, and ranged from 0.44/1000 deliveries to 2.1/1000 deliveries at the individual centres (Table 1). The mean maternal age was 27.8±6.9 years overall (27.5±6.9 years for EOD cases). A slight majority, 46 of 88 (52.3%) of affected pregnancies for whom information was available, was multiparous (one or more previous live births, EOD 33 of 70 [47.1%] versus LOD 13 of 18 [72.2%], P=0.06). The median time to rupture of membranes for 82 (67 EOD and 15 LOD) documented cases was 9.9 h (range 0 to 1246 h; 58.5% of cases ruptured in less than 12 h, 17.1% ruptured between 12 h to 18 h, and 24.4% ruptured after more than 18 h). There was no difference in the median time to rupture of membranes between the EOD cases (11.2 h, range 0 to 1246 h) and the LOD cases (9.1 h, range 0 to 41 h) (P=0.13). Furthermore, there was no difference in the number of cases with membranes ruptured for more than 18 h (EOD 17 of 67 cases [25.4%] versus LOD three of 15 cases [20%], P=0.7).

One (1.3%) of 78 mothers with EOD infants had a pre-

TABLE 3: Clinical risk factors of neonatal group B streptococcal (GBS) disease identified based on delivery mode

	Delivery mode					
	Vaginal n= 76*		Elective caesarean section deliveries n= 10*		Emergency caesarean section deliveries n= 15*	
Clinical risk factor	EOD (%)	LOD (%)	EOD (%)	LOD (%)	EOD (%)	LOD (%)
Intrapartum fever >38°C	9/54 (16.7)	1/12 (8.3)	1/6 (16.7)	1/3 (33.3)	3/10 (30)	1/2 (50)
Chorioamnionitis	6/46 (13.0)	0/10	2/6 (33.3)	0/2	2/10 (20)	0/1
GBS positive status	1/58 (1.7)	1/18 (5.6)	1/6 (16.7)	0/4	1/13 (7.7)	0/2
Prolonged rupture of membranes ≥12 h	20/49 (40.8)	4/11 (36.4)	5/6 (83.3)	0/3	8/11 (72.7)	0/1
Prolonged rupture of membranes ≥18 h	9/49 (18.4)	3/11 (27.3)	2/6 (33.3)	0/3	5/11 (45.5)	0/1
Gestational age <37 weeks	23/53 (43.4)	7/16 (43.8)	6/6 (100)	1/3 (33.3)	7/13 (53.8)	1/2 (50)

**Denominator totals for early-onset disease (EOD) and late-onset disease (LOD) do not always total this number because of missing data*

vious pregnancy complicated by neonatal GBS disease. Chorioamnionitis was identified in 10 (15.9%) of 63 documented EOD cases, and maternal fever was identified in 13 (18.3%) of 71 documented EOD cases . At least one maternal risk factor for neonatal GBS disease was noted in 46 of 78 (59%) infants with EOD. Only seven (9%) mothers with EOD had a history of screening for GBS recorded in their health records (Table 2). If GBS-positive mothers had been included in the at risk group, 55 of 78 (70.5%) of the EOD cases would have been identified prenatally as being at risk. Eighteen (14 of 62 [22.6%] of EOD and 4 of 13 [30.8%] of LOD, P=0.53) of 75 pregnancies for which information was recorded, received one dose of intrapartum antibiotics; no patient received more than one dose of antibiotics. The majority (76 of 105 [72.4%]) of deliveries were vaginal, 10 (9.5%) were by elective caesarian section, and 15 (14.3%) by emergency caesarian section (Table 3). Mothers with fever, preterm labour, chorioamnionitis and prolonged rupture of membranes (more than 18 h) were more likely to have received intrapartum antibiotics (Table 2).

Of the 105 infants identified, 59 (56.2%) were male (EOD, 56.4% male). The mean gestational age at birth was 36.2±4.7 weeks, with 38 of 96 (39.6%) less than 37 weeks (31 of 73 [42.5%] of EOD cases were less than 37 weeks). The median birth weight in 94 documented cases was 3099 g (range 610 g to 4830 g), of whom 30 of 94 (31.9%) were less than 2500 g (23 of 75 [30.7%] EOD cases were less than 2500 g). Fifty-one (48.6%) infants were born at the reporting hospital, 37 (35.2%) at hospitals other than the reporting hospital, one (1%) infant was born at home, while the place of birth was not known for 16 (15.2%) infants. The majority of EOD cases, 78.9% [60 of 76], presented within 24 h of delivery, and 94.7% [72 of 76] within 48 h; the exact time to presentation of illness was not known for two EOD cases. Ninety-nine (94.3%) infants were bactermic, including 74 EOD and 25 LOD cases. Pneumonia was the most common clinical illness (43.8%), followed by bacteremia without focus (23.8%), and meningitis (14.3%). More EOD infants presented with pneumonia than LOD infants (43 of 78 versus three of 27, P<0.001), while more LOD infants presented with meningitis (six of 78 versus nine of 27, P<0.01). The mean duration of antibiotic therapy was 9.3±5.9 days (EOD 8.8±5.9 days versus LOD 10.7±6.0 days, P=0.20), with a median length of stay at participating hospitals of 10 days (range 0 to 892 days). Seventeen (16.8%) infants died (15 of 76 EOD cases versus two of 25 LOD cases, P=0.23); information was unavailable for four cases, at a median of one day (range 0 to 72 days) of life for EOD cases. Prematurity was the only variable among infants presenting with EOD that was associated with increased mortality (Table 4). Maternal intrapartum antibiotic usage was recorded for 14 of the EOD infants who died. These infants did not receive more than one dose of intrapartum antibiotics.

DISCUSSION

Invasive GBS disease remains a significant cause of infectious morbidity in newborn infants (34-35). Our study is important because it is the first national study to examine the burden of illness and presentation of neonatal GBS disease across Canada, and to set the basis for comparisons with international studies and studies within Canada. It is also useful because it presents a baseline for which identified maternal and neonatal risk factors can be targeted for preventive strategies. Although our study was hospital based, the overall rates of EOD cases of 0.44 to 2.1/1000 live births are similar to or lower than rates noted in the United States during a similar period for hospital- and population-based studies (1,24,26,36). Differences with the American findings may be real and due to differences in populations studied or may reflect a bias due to referral in primarily hospital-based studies.

The clinical presentation of neonatal GBS has varied between studies. In our study population, there was a disproportionate percentage of premature (45%) and low birth weight (32%) infants, confirming the known association between prematurity, low birth weight and neonatal GBS disease. The preterm and low birth weight rates among the infants with GBS represent five to seven times what would have been expected in all neonates across Canada (Statscan). The rates of prematurity for EOD cases in our study (42.5%) were intermediate between the

TABLE 4: Case fatality of early-onset neonatal group B streptococcal (GBS) disease cases in the presence or absence of clinical risk factors

Clinical risk factor	Number (%) who died with risk factor*	Number (%) who died without risk factor*	P
Intrapartum fever >38°C	3/13 (23.1)	11/58 (19.0)	0.71
Chorioamnionitis	4/10 (40.0)	10/53 (18.9)	0.21
Intrapartum antibiotics	3/14 (21.4)†	11/48 (22.4)	0.94
Prolonged rupture of membranes			
≥12 h	5/30 (16.7)	8/37 (21.6)	0.76
≥18 h	3/17 (17.6)	10/50 (20.0)	1.00
Gestational age <37 weeks	10/31 (32.3)	4/43 (9.3)	0.02
Birth weight <2500 g	7/23 (30.4)	8/52 (15.4)	0.21
Hours after birth to presentation of infection			
<24 h	11/54 (20.4)	5/16 (31.3)	0.50
<48 h	14/66 (21.2)	0/4 (0)	0.58
Inborn	10/40 (25.0)	3/26 (11.5)	0.18

**Numerator is number who died, denominator is number with clinical feature present or absent. Denominators do not always total 78 because of missing data; †All three who died received only one dose of antibiotics*

rates observed in Atlanta (28%) and Melbourne (79%) (1,31), but similar to rates found by Weisman et al (36) in hospitals across the United States (39%) and rates identified by Faxelius et al (37) in Sweden. Whether prematurity is a risk factor or consequence of GBS infection is currently unclear. Similarly, the rates of low birth weight deliveries of 32% in our cohort, although high, are much lower than the 74% figure noted for all EOD cases in Chicago (19). Our rate of caesarian section deliveries for EOD cases of 24.8% was similar to the rates noted in Chicago (19,7%), Sweden (31%) (37) and across the United States (34%) (36). Of note in our cohort, two-thirds of the caesarian sections were performed by on an emergency basis, suggesting concerns about fetal compromise. Although almost 8% of EOD cases were delivered by elective caesarian section, all had a known risk factor that could have contributed to the development of disease.

The time of presentation of GBS disease in our population was very consistent with previous studies, with at least two-thirds to three–quarters of all cases being EOD (27,29,38). The clinical presentation of pneumonia in 40% and meningitis in about 8% of EOD cases is virtually the same as the 40% and 6.3%, respectively, noted previously by Weisman et al (36), with the majority of cases presenting within the first 24 h of life (29). Although meningitis has traditionally been associated with LOD and occurred in one-third of this group of patients, most patients with this form of GBS infection still present with a clinical picture that does not involve meningitis. The fatality rate in our study of almost 20% for EOD cases is much higher than recent reports of GBS-related fatality from population-based studies (26,27) of 4% to 6% in the United States and closer to rates noted in the 1980s, mostly by hospital-based studies (19,39). This could be partly due to bias because of over-representation of more ill patients in our predominantly tertiary care hospital-based study or may also reflect delayed recognition and lack of adequate early intervention. For EOD cases, the timing of presentation (approximately 79% within 24 h of birth) was similar to the rates noted from previous reports by other groups (19,39). This is clearly an area requiring ongoing monitoring in Canada.

Expert opinion regarding the prevention of neonatal GBS had differed based either on identification of known risk factors for GBS (premature delivery, prolonged rupture of membranes less than 18 h, intrapartum fever, previous infant with GBS, GBS bacteriuria) or screening of pregnant women (32,33,40,41). However, there is now consensus in the United States with all the major expert bodies (Centres for Disease Control and Prevention, American Academy of Pediatrics, and the American College of Obstetrics and Gynecology) recommending that intrapartum antibiotic prophylaxis should be given to either women with known risk factors, or screening at 35 to 37 weeks' gestation with intrapartum antibiotic prophylaxis given to all colonized women, women in preterm labour or women with a previous infant with GBS (33,42-44). There is evidence that both approaches have not been implemented in Canada (23,45,45). Although numerous potential risk factors were identified, no single risk factor could explain the majority of cases in our study. However, 54% of all the EOD cases in our database had at least one identifiable maternal risk factor which would have justified the use of intrapartum antibiotic chemoprophylaxis. A previous decision analysis (47) suggested that up to 69% of GBS cases are preventable using a risk factor based approach. A recent multistate American study (48) found that 44% of EOD cases were preventable. It appears that there was a low rate of screening performed on the mothers of the identified children in our study, or this information was not available in the hospital health records, a factor likely to negatively im-

pact screening based approaches to prevention. This has likely changed significantly and warrants monitoring because all the expert guidelines for GBS prevention were introduced after 1992. Decision analyses have suggested that screening at 35 to 37 weeks' gestation, and giving intrapartum antibiotics to all mothers with preterm deliveries and all GBS carriers, would prevent up to 86% of all EOD GBS cases (30,47). The current screening-based recommendation of the Centers for Disease Control and Prevention, and the American Academy of Pediatrics suggests offering intrapartum penicillin to all colonized women and mothers with preterm deliveries (44). There are some indications (unpublished data from Alberta and Ontario) that screening strategies are being adopted more in Canada, but the actual impact of these strategies remains to be seen.

It is of interest that 24% of all the pregnant mothers who gave birth to an infant with EOD received intrapartum antibiotics. However, all these mothers received only one dose, and all the EOD deaths occurred in infants whose mothers had received one or no doses of antibiotics. There is evidence that at least two doses or more than 4 h of antibiotics are needed to prevent a case of early onset neonatal GBS disease (49,50). Our findings highlight the importance of early recognition of women at risk in labour in order to initiate administration of multiple (more than two) doses of intrapartum antibiotics to effectively reduce the risk of neonatal GBS EOD.

CONCLUSION

In this retrospective cohort study of invasive neonatal GBS infections involving 13 Canadian paediatric secondary and tertiary care hospitals, 105 cases of GBS were identified. Identification of maternal and obstetrical risk factors with use of intrapartum antibiotics may potentially have prevented more than half of the cases. The case fatality rate of affected infants was somewhat higher than would have been expected in 1992, but this may be a reflection of the neonatal population studied. National Canadian consensus preventive guidelines introduced in 1994 (33) and newer American guidelines released in 1996 (44) are likely to have modified the presentation and outcome of neonatal GBS disease in Canada. Having established significant mortality and high morbidity among survivors and identified potential risk factors, attention should now focus on population-based studies to better define the incidence across the country to allow implementation of appropriate prevention strategies.

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