Original Article

Population-based study of early-onset neonatal sepsis in Canada

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Abstract

Objective: To determine the incidence, types of organisms and resistance patterns involved in early-onset neonatal sepsis in Canada.

Study design: Early-onset neonatal sepsis cases were identified through the Canadian Paediatric Surveillance Program. Neonates were excluded if they were asymptomatic or if intracranial procedures preceded a positive cerebrospinal fluid culture.

Results: One hundred and twenty-seven cases were identified (0.17 cases per 1000 live births). Group B Streptococcus accounted for 41.7%, *Escherichia coli* for 35.4%. Antibiotic resistance was present in 33.9% of all cases. 55.6% of *E coli* cases were resistant, most commonly to ampicillin. Infecting organism species were associated with gestational age, being very low birth weight, time at sepsis presentation, maternal antibiotic prophylaxis and rupture of membranes lasting over 18 hours. Group B Streptococcus was most common in term and *E coli* in preterm neonates. Twenty-two per cent of *E coli* cases presented after 48 hours, compared to 6% of Group B Streptococcus cases.

Conclusion: We identify a lower rate of early-onset neonatal sepsis than historically suggested, with differing dominant organisms based on gestational ages and other factors, as well as high rates of resistance especially among *E coli* cases.

Keywords: Antibiotic resistance; *Escherichia coli*; meningitis; neonatal sepsis; Streptococcus Group B.

Neonatal sepsis is defined as a systemic bacterial infection in infants less than 1 month of age and is a significant cause of morbidity and mortality worldwide (1,2). Early-onset neonatal sepsis (EONS) is caused by vertical transmission of infectious organisms from the mother, before or during birth, with nosocomial transmission being rare (3).

EONS has been variably defined, with clinical presentation either at <48 hours (4), <72 hours (5–22) or <7 days (1,2,23–28) after birth. The vast majority (90%) of infants present within

48 hours (8), but the potential for some to present slightly later has prompted organizations, such as the Centers for Disease Control (CDC) and the World Health Organization (WHO), to adopt the <7 days definition. Estimates of EONS incidence range from 0.30 to 1.19/1000 live births (14,17–19,28).

Historically, Group B Streptococcus (GBS) has been implicated as the most common pathogen involved in EONS (26,29). The CDC and the American College of Obstetricians and Gynecologists (ACOG) recommended intrapartum antibiotic

prophylaxis (IAP) to prevent GBS perinatal transmission in 1996, and the Society of Obstetricians and Gynaecologists of Canada (SOGC) adopted congruent guidelines in 1997 (26,30,31). CDC guidelines were further revised in 2002 and 2010, with SOGC and ACOG guidelines revised as well.

Implementation of these guidelines has resulted in a drastic reduction in EONS due to GBS, from 1.3 to 1.7 per 1000 in the early 1990's to 0.3 to 0.6 per 1000 after the guideline implementation (25,26,32,33). Subsequently, there has been a relative increase in EONS caused by other organisms, including Gram-negative species, such as *Escherichia coli* (23). This trend has been reported in Canadian neonatal intensive care units (NICUs) (12) and in some US centres (9,10,13,23). Reports of antibiotic-resistant bacteria causing EONS have been on the rise (10,16).

Despite data from North American hospitals and NICUs (9,10,12,13,23), the rates and organisms involved for the entire population are unknown, as population-level national surveillance data is lacking in Canada and the USA. An improved understanding of the changing patterns in population-level EONS incidence and causative agents may be helpful in evaluating maternal and neonatal guidelines in the post-GBS prophylaxis era (26,34).

The aim of the current study was to determine the incidence of EONS, types of organisms and corresponding resistance patterns involved in EONS in Canada, and to determine if pathogens are associated with specific risk factors.

METHODS

A prospective observational study was conducted through the Canadian Paediatric Society Surveillance Program (CPSP) between January 1, 2011 and December 31, 2012. The CPSP is a national surveillance program in operation since 1996 that tracks multiple paediatric illnesses, and has been externally evaluated previously (35). Each month, the CPSP sends a surveillance survey to all 2500 Canadian paediatricians including paediatric subspecialists (35,36). Details of CPSP's surveillance methods have been published elsewhere (35,36).

Each physician reporting cases which met the case definition (below) were asked to complete a questionnaire developed for this study, including: case-specific demographic information; maternal factors predisposing to newborn infections; family history; medical history; laboratory investigations and treatment and outcome (Supplementary Information 1) (37). Of the physicians that reported cases, 81% completed the detailed questionnaires for both years (38,39). Potential risk factors were assessed but some were not statistically significant: maternal GBS, maternal urinary tract infection (UTI), maternal temperature more than 38°C, elevated maternal white blood cell (WBC) count (>10,000 after the onset of

labour), clinical diagnosis of chorioamnionitis, mode of delivery, 5-minute APGAR score <7 and male gender (26,31). Research Ethics Board approval for this study was obtained through St. Michael's Hospital, Toronto, Ontario.

Case definition

Neonates were eligible for inclusion if they presented at less than 7 days of age with either a positive blood culture and/or a positive cerebrospinal culture (CSF) from a lumbar puncture.

Neonates were excluded if

1. They were asymptomatic with a positive blood or CSF culture likely to be a contaminant (i.e., coagulase-negative *Staphylococcus* (40), *Diphtheroids* (41), *Corynebacterium* spp (40), *Bacillus* spp, *Propionibacterium* spp, *Aerococcus* spp (42,43) or *Micrococcus* spp (14,18,41); or,
2. The neonate had a positive CSF culture as a result of a drain, reservoir, shunt or intracranial surgical procedure

Statistical analysis

Research assistants entered the data into an Excel spreadsheet. Random checks to determine the data entry accuracy were conducted by senior researchers to ensure reliability. Data for the general population were obtained from Statistics Canada (43), with all data from 2011 and 2012, with the exception of multiple births (twins). Twin births data from 2012 were lacking at time of analysis, thus 2010 and 2011 data were used instead. Chi-square tests were used to compare the proportion of infant characteristics in the sample with the distribution observed in the general population of Canada. When numerators were less than 5, we used Fisher's exact test for proportions. Fisher's test was also used to compare the distribution of bacteria and risk factors. All P-values were two-sided and values less than 0.05 were considered to reflect associations beyond chance. SAS 9.4 was used for statistical analysis.

RESULTS

Over the 2-year study period, 214 cases of EONS were reported to the CPSP, of which 127 were confirmed to be true cases of EONS, as per the case definition and exclusion criteria (Table 1). The remaining 87 cases were excluded for the following reasons: duplicate reporting (n=11); did not fulfill the case definition (n=33) and insufficient information to confirm a case diagnosis (n=43). The estimated incidence of EONS for 2011 and 2012 was 0.17 per 1000 live births in Canada.

Mean gestational age (GA) at birth was 34 weeks (SD=5.7), with 48% full term (37 to 41 weeks). Mean birth weight was 2434 g (SD=1162 g). A total of 32% of births were by Caesarean section, with the majority of these Caesarean sections (83%) preceded by one or more signs of maternal infection. A total

Table 1. Baseline demographics

Demographics		Number	%
Lab-confirmed EONS cases	Positive blood or CSF cultures	127	100
	Positive blood cultures only	109	86
	Positive CSF cultures only	5	4
Incidence of sepsis in Canada (per 1000 live births)*		0.17	-
Gestational age at birth	Mean weeks (SD)	34 (5.7)	-
	<32 weeks	41	32
	32–36 weeks	24	19
	37–41 weeks	61	48
	Unknown	1	1
Birth weight	Mean (SD), g	2434 (1162)	-
	VLBW (<1500 g)	34	27
	Unknown	4	3
Male		76	60
Twins		3	2
5 min APGAR<7 (5 unknown)		39	30
Meningitis		18	14
Mode of delivery	Vaginal birth	85	67
	C-section	40	32
	Instrumental delivery	9	7
	Unknown	2	2
Maternal risk factors	Prolonged ROM (7 unknown)	40	32
	Chorioamnionitis (8 unknown)	30	24
	Maternal GBS (48 unknown)	1	1
	Maternal UTI (25 unknown)	13	10
Gravida, mean (SD) (7 unknown)		2.4 (1.7)	-
Maternal ethnicity	Caucasian	59	47
	Black	13	10
	Indigenous Peoples	16	13
	East Indian	7	6
	West Asian	8	6
	Unknown	24	19

*Denominator is 759,505 total Canadian live births according to Statistics Canada in 2011 and 2012 (ref. 43).

CSF Cerebrospinal fluid; EONS Early-onset neonatal sepsis; GBS Group B *Streptococcus*; ROM Rupture of membranes; UTI Urinary tract infection; VLBW Very low birth weight

of 18 neonates (14%) had meningitis, as ascertained by a positive CSF culture (Table 1). Ten per cent of mothers in our population were identified as black. Comparatively, 3.5% of women of child bearing age (15 to 44 years) were black in the 2011 Canadian census (44). The majority (80%) of cases of EONS presented within 24 hours of birth. Relative to the Canadian birth cohort, the EONS cases population had a significantly higher proportion of males ($P<0.001$), premature births ($P<0.001$) and very low birth weights (VLBW; <1500 g) ($P<0.001$) (Supplementary Information 2).

GBS was the most frequently isolated organism from EONS blood or CSF cultures (42%), followed by *E. coli* (35%) (Table 2). One-third (34%) of total cases were resistant to one

or more antibiotics, with the majority occurring among Gram-negative species (Table 2). *E. coli* was most commonly resistant to ampicillin (49%), followed by gentamicin (11%). Two *E. coli* and one *Haemophilus influenza* case produced extended-spectrum beta lactamase (ESBL). While no penicillin resistance was noted in GBS cases, 11% were resistant to clindamycin and 9% to erythromycin. Other resistance data are available in Table 2.

Infecting organism species were associated with the neonate's GA ($P<0.001$); being VLBW ($P=0.02$); time at sepsis presentation ($P=0.024$); maternal IAP given ($P=0.003$) and rupture of membranes lasting more than 18 hours (prolonged ROM) ($P=0.007$). GBS was most common in term neonates, while *E. coli* was most common in preterm

Table 2. Types of bacteria and resistance data according to gestational age at birth

Organism			<32 weeks	32–36 weeks	≥37 weeks	Unknown	Total (%) [†]
Group B streptococcus	N (% of total Group B streptococcus cases)		12 (23)	4 (8)	36 (68)	1 (2)	53
	Resistance (% of organism-specific cases)	Yes	1 (8)	-	9 (25)	-	10 (19)
		No	9 (75)	3 (75)	27 (75)	1 (100)	40 (76)
		Unknown	2 (17)	1 (25)	-	-	3 (6)
<i>Escherichia coli</i>	N (% of total <i>E coli</i> cases)		21 (47)	12 (27)	12 (27)	-	45
	Resistance (% of organism-specific cases)	Yes	12 (57)	6 (50)	7 (58)	-	25 (56)
		No	8 (38)	4 (33)	5 (42)	-	17 (38)
		Unknown	1 (5)	2 (17)	-	-	3 (7)
Other gram positives*	N (% of total other gram positive cases)		4 (19)	8 (38)	9 (43)	-	21
	Resistance (% of organism-specific cases)	Yes	-	4 (50)	-	-	4 (19)
		No	4 (100)	4 (50)	8 (89)	-	16 (76)
		Unknown	-	-	1 (11)	-	1 (5)
Other gram negatives**	N (% of total other gram negative cases)		5 (56)	-	4 (44)	-	9
	Resistance (% of organism-specific cases)	Yes	4 (80)	-	1 (25)	-	5 (56)
		No	1 (20)	-	3 (75)	-	4 (44)
		Unknown	-	-	-	-	-
Total	N (% of all cases)		41 (32)	24 (19)	61 (48)	1 (1)	127 (100)
	Resistance (% of all cases)	Yes	16 (39)	10 (42)	17 (28)	-	43 (34)
		No	22 (54)	11 (46)	43 (71)	1 (100)	77 (61)
		Unknown	3 (7)	3 (13)	1 (2)	-	7 (6)

*Other Gram positives includes: *Streptococcus pneumoniae*, *Streptococcus bovis*, *Streptococcus anginosus*, *Streptococcus mitis*, *viridans streptococci*, *Streptococcus pyogenes*, alpha-haemolytic streptococcus, *Bacillus cereus*, *Enterococcus faecalis*, coagulase negative staphylococcus, *Staphylococcus epidermidis*, *Staphylococcus warneri*, *Staphylococcus aureus*

**Other Gram negatives includes: *Haemophilus influenza*, *Pseudomonas aeruginosa*, *Citrobacter koseri*, *Citrobacter freundii*

[†]Organism was significantly associated with gestational age (<37 weeks and ≥37 weeks) (P<0.001)

(P<0.001) and VLBW neonates (P=0.022). The rate of EONS due to *E coli* in VLBW neonates was 2.63/1000 live births. Most cases of GBS (94%) and *E coli* (76%) presented within 48 hours. Half of *E coli* cases (47%), versus 21% of GBS cases, were preceded by prolonged ROM. The mother received IAP in a majority of *E coli* cases (62%) and 25% of GBS cases (Table 3).

The overall case fatality rate for EONS was 11% (14 deaths); 17% and 3% among preterm and term cases, respectively. *E coli* was identified in 11 deaths (79%) and had a case fatality rate of 24%. Six deaths from *E coli* cases were resistant to ampicillin at minimum, or in addition to other antibiotics. Seven of the *E coli* cases were in neonates less than 32 weeks gestation.

DISCUSSION

In this national surveillance study, the estimated incidence of EONS for 2011 and 2012 was 0.17/1000 live births in Canada. GBS was isolated in 42% and *E coli* in 35% of EONS cases;

the latter was most common in premature infants. One-third of the cases were caused by organisms resistant to at least one antibiotic. Apart from gestational age, the species of infecting organism was significantly associated with time at sepsis presentation, the mother having received GBS prophylaxis, and rupture of membranes lasting more than 18 hours.

The overall incidence of EONS is lower than suggested by previous studies, which quote ranges from 0.58 to 0.98/1000 live births (4,5,14,17,18,24,25). Some of the differences could be accounted for by tertiary centre and/or referral centre bias, or could be figures extrapolated from single centre data (18,19). A US national population-based study identified a rate of GBS EONS at 0.40 per 1000 live births in 2006 (25). A recent large cohort study reported an incidence of 0.3 per 1000 live births but excluded preterm infants (28). It is unclear why our incidence of EONS may be lower; however, it may reflect a continuation of the trend of decreasing EONS due to the ongoing use of antibiotic prophylaxis (intrapartum and postpartum) (26,28,31).

Table 3. Risk factors and types of bacteria

Risk factors*		Group B streptococcus	Other Streptococcus	Other Gram positives	<i>Escherichia coli</i>	Other gram negatives	Total	P-value***
Prolonged ROM		11	5	-	21	3	40	0.0069
Maternal antibiotics (GBS prophylaxis) given:	Yes	13	2	5	28	3	51	0.0037 [†]
	No	28	10	3	13	4	58	
	Unknown	12	-	1	4	1	18	
VLBW (<1500 g)		9	1	3	20	1	34	0.0224
Time at sepsis presentation**:	<24 h	45	11	4	34	7	101	0.0243
	24–48 h	5	-	-	-	-	5	
	48–72 h	1	-	-	1	-	2	
	72 h to 6 days	2	1	5	10	1	19	
Total		53	12	9	45	8	127	-

Major organisms under streptococcus are *Streptococcus pneumoniae* and major organisms under gram negative are *Haemophilus influenzae*.

*Other risk factors that were included but did not reach significance: maternal Group B *Streptococcus*, maternal urinary tract infection, maternal temperature more than 38°C, elevated maternal white blood cell count, chorioamnionitis, mode of delivery, 5 min APGAR <7, male gender.

**Time at sepsis presentation was determined using the number of days between birth and when blood culture drawn, or if not available, then the reported time at sepsis presentation.

***Fisher's exact test for proportions

[†]Fisher's exact test was performed after excluding unknown values.

GBS Group B *Streptococcus*; ROM Rupture of membranes; VLBW Very low birth-weight

Although these studies indicate an ongoing predominance of GBS in EONS, a recent national-level Canadian study (2012), that exclusively focused on level III NICUs during two time periods, found *E coli* to be more common (12). This study identified that GBS accounted for 24.4% of EONS cases in 2003 to 2005 and 16.3% in 2006 to 2008. *E coli* cases outnumbered GBS cases in 2006 to 2008 at 26.4%, which had increased from 22.8% in 2003 to 2005. The discrepancy may be explained by differences between the study populations. The NICU population was of younger gestational age (63% versus 51%, <37 weeks) in the previous Canadian study (12). Similar reports with VLBW infants have also been identified in NICUs and neonatal centres in the USA (5,9,11,13,14,18), Europe (6), and Israel (15) and Australia (4). Additionally, our low number of coagulase negative staphylococcus among symptomatic preterm infants has been identified by others (9) and may reflect improved hospital infection-prevention practices compared to prior studies (6,9).

Our case fatality rate was 11% overall and 24% among *E coli* cases. Population-based studies in the US identified similar rates (5,14,25). A slightly higher overall EONS case fatality rate has been reported in NICU based studies (4,18,22,45). The risk of death was not higher in *E coli* than GBS cases after adjusting for GA in the US study, suggesting that *E coli*'s high fatality rate in our study may be due to the younger gestational age of *E coli* cases, rather than the increased fatality of the *E coli* organism (14,25).

In our study, time at sepsis presentation was significantly associated with the species of infecting organism. A total of 85% of GBS cases presented within 24 hours. Furthermore, 94% of

GBS cases and 76% of *E coli* cases presented within 48 hours, while 4% of GBS and 22% of *E coli* cases presented between 72 hours and 6 days. The tendency for GBS to present within 24 hours has been previously identified in US studies (20,25,46) and serve as the basis for current Canadian treatment guidelines, which recommend limiting the observation of infants to 24 hours when born to a GBS-positive mother who did not receive adequate IAP (34). National laboratory data from England and Wales also support the relatively early presentation of GBS (47). Our study is one of the first to provide population-level clinical data on time at sepsis presentation for EONS cases due to organisms other than GBS (28). *E coli* cases may be presenting later due to nosocomial infection, since preterm neonates in whom *E coli* was more common tend to spend longer in the NICU. Nevertheless, given the substantial proportion of EONS cases caused by *E coli*, and the tendency for *E coli* to present later than GBS, further research is indicated to address whether infants at higher risk of *E coli* should be observed for longer than the currently recommended 24 hours.

Our study reaffirms that resistance is an important factor at the population level. Half of the *E coli* strains causing EONS in our study were resistant to ampicillin, with an additional two cases producing ESBL, and 11% were resistant to gentamicin. This value is lower than that reported by a single-centred tertiary-level NICU in Canada in the late 1990's, with *E coli* resistant to ampicillin in 75% of cases and gentamicin in 50% of cases of EONS (16). A population-based surveillance study of EONS in the US found ampicillin resistance in 66% of *E coli* strains

among EONS cases in 2005 to 2014 (5), with similar rates in Connecticut (24). Emergence of ESBL among *E coli* and other Gram-negative EONS pathogens has also been identified in India (20) and Germany (48) and may further complicate the empiric selection of antibiotics.

Our study identified meningitis in 14% of EONS cases, compared to 6% of EONS cases between 2006 and 2008 in Canadian NICUs (12). The majority of our cases were due to GBS (72%), while in the earlier study the numbers of GBS (25%) and *E coli* (21%) meningitis were similar. This difference may be explained by gestational age and greater prevalence of GBS in term infants. US and Australasian NICU studies identified lower meningitis rates among EONS cases overall (18) and EONS due to *E coli* (4).

The limitations of using voluntary reporting methods should be considered when interpreting these results. Close to 80% of paediatricians reported to the CPSP during our study time period, but it is possible that this is an underrepresentation. Despite attempts to contact all reporting physicians, not all cases had full information for a more detailed analysis. Although our data completion for antibiotic resistance (95%) was encouraging, we did not have direct access to laboratory results. The relatively small number of resistant bacterial species precluded in-depth antibiotic resistance analysis. The paediatricians reporting cases may have had limited access to maternal history and clinical management, therefore maternal data including chorioamnionitis may have been under-reported. Another limitation was the reliance on reported blood and CSF cultures for confirmation of sepsis, which has limited sensitivity (49). Finally, the strict exclusion criteria may have resulted in a conservative estimate of incidence, as we excluded asymptomatic neonates with a culture likely to be a contaminant (including CoNS (5,40)), and neonates with a positive CSF culture as a result of an intracranial procedure.

CONCLUSIONS

In this study, the incidence of EONS was lower than historical studies which reinforces the benefits of IAP in reducing EONS. Organisms differed based on gestational age; GBS was more common among term infants and *E coli* was more common among preterm infants. Antibiotic resistance was higher than previously reported with the majority of *E coli* being resistant to ampicillin and gentamicin, and occurring in preterm infants. Finally, the significant proportion of cases caused by *E coli*, and their tendency to present later than EONS due to other organisms, raises the question of whether neonates at risk should be observed for longer than 24 hours. Further research is required in order to reassess treatment recommendations in centres with higher rates of antimicrobial resistance.

Supplementary Material

Supplementary data are available at *Paediatrics & Child Health Online*.

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The authors have no financial relationships relevant to this article to disclose.

Ethics approval

Research ethics board approval for this study was obtained through St. Michael's Hospital in Toronto, Ontario.

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Conflict of Interest

The authors have no conflicts of interest relevant to this article to disclose.

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