Necrotizing Enterocolitis in Neonates Admitted to Alberta Neonatal Intensive Care Units

Purpose

Necrotizing enterocolitis (NEC) is a serious gastrointestinal disease in newborns and mainly affects those in neonatal intensive care units (NICU) (1). NEC is characterized by inflammation that causes damage to the intestinal tract. The incidence of the disease has been reported from less than 1 per cent to 5 per cent of admissions to NICU, and between 0.5 and 5 cases per 1,000 live births (2).

NEC affects mostly premature babies or babies of low birth weight. NEC typically occurs in the first weeks after birth in the neonate who is premature and has been formula fed. Symptoms of NEC may include vomiting, diarrhea, bloody stool, feeding intolerance, swollen abdomen, and absence of bowel sounds. It may therefore be difficult to distinguish mild cases of NEC from other gastrointestinal conditions, such as cow's milk protein intolerance. Advanced cases may show fluid in the peritoneal (abdominal) cavity, bowel perforation, peritonitis (infection of the membrane lining the abdomen), or shock. Mortality rates from NEC range from 15% to 30% (2). Most NEC cases are treated medically, but severe cases may require surgical removal of the dead bowel tissue.

The causes for NEC are not known. Most cases of NEC appear to be sporadic, but outbreaks in neonatal units have been reported (3, 4). The observation of clustering of cases suggests possible infectious etiology, and yet no single one infectious agent has been consistently linked to the outbreaks of NEC (2).

NEC is a serious disease in newborns. It is important to understand the epidemiology of NEC in Alberta - determine the extent of the disease, and identify any risk factors that are preventable through public health intervention. In this *Public Health Surveillance Bulletin*, we report the incidence and identify potential risk factors for NEC based on a population-based cohort of neonates admitted to Alberta NICUs between 2006 and 2011. We identified NEC cases from the hospital discharge abstract database using diagnostic codes (ICD10-CA P77), and included all stages of NEC (mild to advanced) reported by clinicians.

Key Findings

Between 2006 and 2011, 1.2 per cent of the neonates admitted to the NICU developed NEC. The incidence of NEC in Alberta is 1.7 cases per 1,000 live births. About 7 per cent of NEC cases died within 30 days after birth. About 90 per cent of NEC cases were born preterm (gestational age less than 37 weeks) or of low birth weight (less than 2500 grams). The risk of developing the disease is inversely related to gestational age and birth weight. Feeding with mother's own milk or breastfeeding is associated with a decreased likelihood in developing NEC in neonates.

Applications

Prematurity and low birth weight are risk factors significantly associated with development of NEC, whereas breast milk feeding has been shown to be protective against NEC. An immediate and effective strategy to reduce the risk of NEC is to actively promote provision of mother's own milk to premature babies, particularly in NICU's where breastfeeding rates are lower than in the general population. Longer-term interventions addressing prematurity and low birth weight are complex, and require a cross-ministry approach.

Methods

All babies born between 2006 and 2011 in Alberta who were admitted to NICU at aged 0 to 30 days were extracted from the hospital discharge abstract database. Infants with at least one International Classification of Diseases, 10th Revision, Canadian Adaptation (ICD-CA) diagnostic code for NEC (ICD10-CA P77 - necrotizing enterocolitis of newborn) were classified as a case. Infants' characteristics including sex, gestational age, birth weight and small for gestational age, as well as pregnancy type (single or multiple), mother's age were extracted from the Alberta Vital Statistics birth registration database. Apgar scores, breastfeeding and maternal factors including alcohol consumption, smoking and drug use during pregnancy, and delivery mode were extracted from the Notice of Birth (NOB) database.

Comparisons of these characteristics between NEC and non-NEC babies were conducted using Chi-square or Wilcoxon test, as appropriate. Multiple logistic regression was used to identify risk factors for NEC. All variables shown to have a p-value of <0.2 in univariate analyses were entered into the model. Backward selection was performed to identify factors significantly associated with NEC.

Results

NEC in Alberta

Between 2006 and 2011, there were 40,178 neonates admitted to NICU; 491 of them (1.2 per cent) had a diagnosis of NEC. The incidence of the disease ranged from 0.7 to 1.5 per cent of NICU admissions or between 1.0 and 2.1 per 1,000 live births during the study period (Table 1). The one-year mortality in this cohort of NICU neonates was 1.3 per cent. It was significantly higher in those with NEC (9.4 per cent), compared with those without the disease (1.2 per cent). Among the 491 NEC cases, 33 (6.7 per cent) died within 30 days after birth.

Table 1: Number and incidence of NEC cases in Alberta, 2006 - 2011

| Year	Number of live births	NICU admissions	NEC cases	NEC cases per 100 NICU admissions	NEC cases per 1,000 live births
2006	45 094	6 683	46	0.7	1.0
2007	48 839	7 015	71	1.0	1.5
2008	50 551	7 071	107	1.5	2.1
2009	51 493	6 754	89	1.3	1.7
2010	50 619	6 357	81	1.3	1.6
2011	50 842	6 298	97	1.5	1.9
Total	297 438	40 178	491	1.2	1.7

Risk factors

Of the 40,178 neonates, 34,985 (87 per cent) were successfully linked to both Vital Statistics and Notice of Birth databases to extract the infants' and maternal characteristics. Among these 34,985 neonates, 376 (1.1 per cent) had a diagnosis of NEC. Subsequent analyses were conducted based on these 34,985 neonates.

About 90 per cent (341/376) of neonates with NEC were born preterm with gestational age less than 37 weeks. The risk of developing the disease is inversely related to gestational age (Figure

1). Over 10 per cent of preterm infants born before 28 weeks of gestation developed NEC. This proportion dropped to 4.5 per cent in infants born between 28 and 32 weeks. The inverse relationship is also shown with birth weight (Figure 2). Of the infants with extremely low birth weight (less than 1,000g), 11.3 per cent had a diagnosis of NEC. This proportion dropped to 5.9 and 1.5 per cent in babies with very low birth weight (1,000-1,500g) and low birth weight (1,500-2,500g) respectively.

Figure 1: Proportion of NICU neonates developing NEC by gestational week
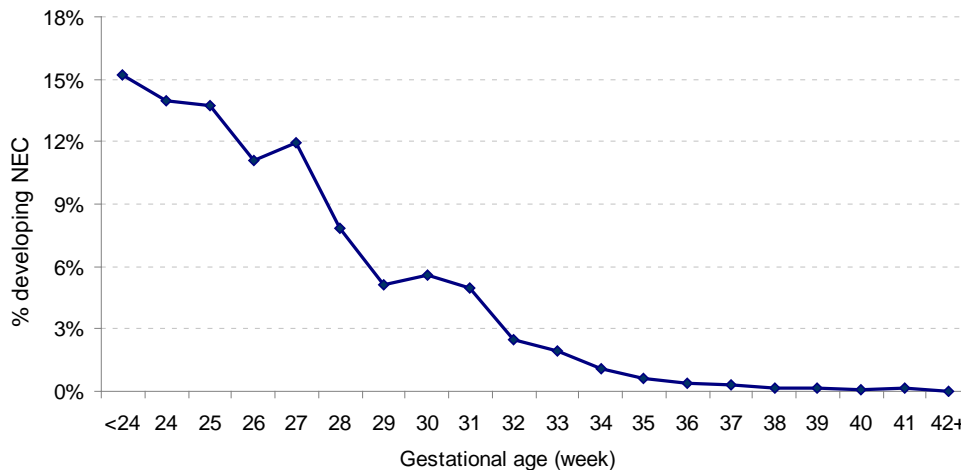
Figure 2: Proportion of NICU neonates developing NEC by birth weight
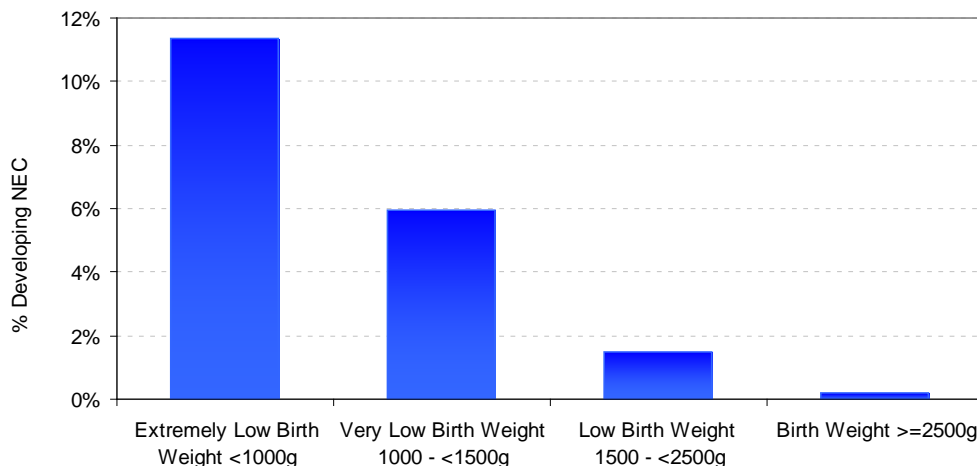

Table 2 summarizes the characteristics of neonates with and without NEC. The neonatal factors significantly correlated with NEC were lower gestational age, lower birth weight, lower Apgar scores, being part of a multiple birth and First Nations. The proportion of breastfed babies developing NEC was significantly lower (0.4 *vs* 1.8 per cent). Maternal factors associated with NEC were age, and smoking during pregnancy.

The multiple logistic regression analysis showed that the risk factors for NEC were lower gestational age, lower one-minute Apgar score, and not feeding with breast milk (Table 3). Compared with a full-term baby of gestational age 37 weeks and older, the risk for a preterm baby born before 33 weeks to develop NEC was 27 times higher and the risk was 5 times higher in a preterm baby born between 33 and 36 weeks. Babies who are fed breast milk had an estimated 40 per cent risk reduction for NEC.

Table 2: Characteristics of neonates admitted to the neonatal intensive care unit (NICU) with and without necrotizing enterocolitis (NEC)

Variable	Non-NEC N=34609	(%)	NEC N=376	(%)	p-value
Infant Characteristics					
Gestational age (week)					
<33	3677	(10.6%)	247	(65.7%)	<0.01
33-36	10539	(30.5%)	94	(25.0%)	
37+	20393	(58.9%)	35	(9.3%)	
Birth weight (g)					
<1000	766	(2.2%)	98	(26.1%)	<0.01
1000 - <1500	1457	(4.2%)	92	(24.5%)	
1500 - <2500	9342	(27.0%)	140	(37.2%)	
≥ 2500	23044	(66.6%)	46	(12.2%)	
Sex (female)	15296	(44.2%)	160	(42.6%)	0.52
Small for gestational age					
No	29289	(85.2%)	321	(86.1%)	0.64
Yes	5085	(14.8%)	52	(13.9%)	
Unknown	235		3		
Apgar at 1 minute*, median (IQR)	8	(6 - 9)	6	(3 - 8)	<0.01
Apgar at 5 minute*, median (IQR)	9	(8 - 9)	8	(6 - 9)	<0.01
Pregnancy type					
single	30086	(86.9%)	278	(73.9%)	<0.01
multiple	4523	(13.1%)	98	(26.1%)	
First Nations	2713	(7.8%)	42	(11.2%)	0.02
Maternal Characteristics					
Age					
<20	1492	(4.3%)	20	(5.3%)	0.05
20-24	6018	(17.4%)	63	(16.8%)	
25-29	10779	(31.1%)	101	(26.9%)	
30-34	10242	(29.6%)	106	(28.2%)	
35+	6078	(17.6%)	86	(22.9%)	
Breastfeeding	17775	(51.4%)	68	(18.1%)	<0.01
Caesarean delivery					
No	15151	(49.1%)	154	(45.2%)	0.15
Yes	15691	(50.9%)	187	(54.8%)	
Unknown	3767		35		
Alcohol consumption during pregnancy					
No	30747	(94.0%)	319	(92.5%)	0.25
Yes	1977	(6.0%)	26	(7.5%)	
Unknown	1885		31		
Smoking during pregnancy					
No	26050	(79.1%)	260	(73.9%)	0.02
Yes	6890	(20.9%)	92	(26.1%)	
Unknown	1669		24		
Drug use during pregnancy					
No	31419	(95.4%)	328	(93.2%)	0.05
Yes	1530	(4.6%)	24	(6.8%)	
Unknown	1660		24		

* 3211 and 2730 neonates with missing apgar scores at 1 minute and 5 minute respectively

Table 3: Risk factors for necrotizing enterocolitis (NEC) - logistic regression analysis

Variable	Odds Ratio	(95% Confidence interval)	
Gestational age (week)			
<33 vs 37+	26.82	(18.09	- 39.78)*
33-36 vs 37+	4.73	(3.11	- 7.19)*
Apgar score at one minute	0.88	(0.84	- 0.93)*
Breastfeeding	0.60	(0.46	- 0.80)*

*p <0.001

Discussion

Similar to other epidemiological reports, NEC affected mostly premature infants, with the risk inversely related to gestational age and birth weight. The etiology of NEC remains poorly understood. Premature infants are at elevated risk of NEC because of developmental immaturity in gastrointestinal motility and digestion, intestinal circulation regulation, intestinal barrier function and immune defense; and other contributing factors include hypoxic-ischaemic injury, feeding with formula and colonization by pathological bacteria (2). In addition, NEC babies were also more likely to have a lower one-minute Agpar score. Apgar at one-minute provides an overall assessment of a newborn's physical health at birth. This suggested that NEC is more common in babies who are sick at birth.

Clinically, NEC is classified based on Bell stage criteria (5), with stage I being a suspected case, and stage II and III a definite and an advanced case respectively. In this study, we used disease coding from the hospital discharge records to identify NEC cases, and were unable to identify the staging of these cases. A study based on the neonates admitted to 25 NICUs within the Canadian Neonatal Network showed that 5.1 per cent of preterm babies with gestational age less than 33 weeks had NEC stage 2 and above (6). The present study showed that 6.3 per cent of the preterm babies in the same group had a diagnosis of NEC. This suggested that the NEC cases identified in this study are likely to represent the cases in all three stages, this is in contrast to many published studies which defined a case of NEC based on stage II and above.

Feeding breast milk has been shown to be protective against NEC, and this is consistent with other reports (7,8). The risk for NEC is significantly lower in exclusively breastfed babies compared with formula-fed babies (9,10). Feeding human milk promotes an improved host defense and gastrointestinal maturation compared with feeding of formula (11). Mothers of preterm infants produce milk with nutritional composition that matches the needs of their premature infants (12). Therefore, an important strategy to reduce the risk of NEC is to promote provision of mother's own milk to premature babies.

Based on the Canadian Community Health Survey (CCHS) 2009, the breastfeeding rate for Albertan mothers was 92.4% (13). This is higher than the breastfeeding rate of 83.7% for all live births 2006-2011 based on our data from the NOB database. The breastfeeding rates presented in this study are likely to be under-estimated, as we have assumed all 'No Answer' as 'No'. Despite the limitation, the data indicates that the breastfeeding rate of NICU babies (51.0%) was likely to be significantly lower than that of the general population (83.7%). Preterm infants are often fed using oro- or nasogastric tubes, receiving a combination of human milk and artificial feeds. Observational research suggests that the greater the proportion of human milk in the diet the lower the risk of NEC. Feeding preterm babies under intensive care with their mothers' own milks presents unique challenges including establishing and maintaining milk supply. Research to understand the barriers, and programs to promote and support breastfeeding and early breast milk expression are needed.

First Nations babies appeared to be more likely to develop NEC than non-First Nations babies (1.5 *vs.* 1.0 per cent, p <0.05). However, after adjusting for confounding in the logistic regression

analysis, being First Nations is no longer found to be a significant risk factor. In this study cohort, 41.4 per cent of non-First Nations were born preterm, compared to 43.7 per cent of First Nations babies (p <0.05). In addition, about 51.6 per cent of non-First Nations babies were breastfed, but only 44.0 per cent of First Nations babies were breastfed (p <0.05). The apparent higher incidence of NEC in the First Nations population may be attributed to a higher rate of prematurity and a lower breast-feeding rate in this group. In the literature, no consistent association between race or socioeconomic status and NEC has been identified.

A strength of this analysis is the inclusion of all neonates admitted to the NICU in Alberta. The population-based nature of the administrative databases limits the selection bias that may occur with single-center studies. However, data such as date of disease onset and clinical staging are not available, and these may limit the epidemiological analyses. Preterm infants are often tube fed receiving a combination of human milk and supplementary feeds. However, the types of supplementary feeds provided are not available in this analysis, thus limiting us to assess the association of NEC with types of alternative or supplemental feeds. A further limitation of this report is that other interventions that might influence the incidence of NEC, such as vascular access procedures and intravenous medications, have not been included in the analysis.

In summary, the epidemiology of NEC in Alberta is similar to published reports. Prematurity and low birth weight are risk factors significantly associated with NEC. Breastfeeding appears to decrease the likelihood of developing NEC. Provision of mother's own milk to premature babies should be actively promoted and supported as a key strategy to prevent NEC. Early breast milk expression is important to mothers of preterm infants. Longer-term interventions addressing prematurity and low birth weight are also needed, and require across-ministry approach.

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