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Other Conditions

Neurodevelopmental and growth outcomes of extremely preterm infants with necrotizing enterocolitis or spontaneous intestinal perforation☆,☆☆,★

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ABSTRACT

Purpose: To evaluate neurodevelopment and growth in extremely preterm infants with or without necrotizing enterocolitis or spontaneous intestinal perforation.
Methods: We conducted a retrospective cohort study of infants admitted to Canadian neonatal intensive care units in 2010 to 2011. We assessed outcomes at 18 to 24 months' corrected ages for preterm infants <29 weeks of gestational age at birth with spontaneous intestinal perforation or non-perforated or perforated necrotizing enterocolitis, and for preterm infants with none of these gastrointestinal complications. The primary outcome was a composite of death or significant neurodevelopmental impairment at 18 to 24 months' corrected age. We used multivariable logistic regression models to adjust for gestational age, small for gestational age, prenatal steroids, cesarean section, multiple gestations, and SNAP-II score.
Results: Of 2,019 infants total, 39 (1.9%) had spontaneous intestinal perforation, 61 (3%) had perforated necrotizing enterocolitis, and 115 (5.7%) had non-perforated necrotizing enterocolitis. Infants with spontaneous intestinal perforation (aOR 2.11; 95% CI 1.01–4.42), necrotizing enterocolitis (aOR 2.58; 95% CI 1.81–3.68), or any bowel perforation (aOR 3.97; CI 2.43–6.48) had higher odds of death or significant neurodevelopmental impairment compared to infants with none of these bowel diseases.
Conclusions: Spontaneous intestinal perforation, necrotizing enterocolitis, or any bowel perforation are risk factors for death or significant neurodevelopmental impairment in extremely preterm infants.
Level of Evidence: Study type: prognosis study (cohort study: retrospective)
Level of evidence rating: II

Abbreviations: NEC, necrotizing enterocolitis; SIP, spontaneous intestinal perforation; CNN, Canadian Neonatal Network; CNFUN, Canadian Neonatal Follow-Up Network; Bayley-III, Bayley Scales of Infant and Toddler Development – Third Edition; CP, cerebral palsy; GMFCS, Gross Motor Function Classification System; ROP, retinopathy of prematurity; BPD, bronchopulmonary dysplasia; NICU, Neonatal Intensive Care Unit; NDI, neurodevelopmental impairment; sNDI, significant neurodevelopmental impairment; SNAP-II, Score for Neonatal Acute Physiology Version II; aOR, adjusted odds ratio; CI, confidence interval; ELBW, extreme low birth weight.

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Necrotizing enterocolitis (NEC) and spontaneous intestinal perforation (SIP) are two significant gastrointestinal complications associated with preterm birth: NEC is associated with systemic inflammation and in severe cases extensive bowel disease [1], whereas SIP happens in a localized area of the gut [2] and is usually not associated with systemic inflammation [3]. Differences in neonatal morbidities and mortality for infants with NEC or SIP have been reported previously [4–6]. Compared to infants without NEC or SIP, affected infants have higher mortality rates during the neonatal period, and surviving infants with NEC or SIP often have potentially higher morbidity and mortality rates [4].

The neurodevelopmental outcomes of preterm infants with these gastrointestinal co-morbidities have previously been published, but some aspects have been more frequently reported than others. Limitations of existing data include small sample sizes regarding SIP [7], lack of comparison between NEC and SIP [8] or of distinction between the 2 entities [9], lack of information regarding components of neurodevelopmental domains [10], and non-adjustment for confounders such as gestational age [8]. These aspects of information can be valuable for understanding the trajectory of NEC and SIP, identifying challenges for children earlier, and potentially suggesting new interventions. Our group has reported data about the epidemiology of NEC and SIP and associated neonatal mortality and morbidity outcomes [4]. This article will extend these data to consider neurodevelopmental outcomes. Our objective in this study was to characterize, in a national cohort, the neurodevelopmental outcomes of preterm infants <29 weeks' gestation who developed SIP, perforated NEC, or non-perforated NEC; and compare those outcomes with those of neonates without these complications.

1. Subjects and methods

1.1. Study design and eligibility criteria

This was a multicenter retrospective study of a cohort of infants admitted to units enrolled in the Canadian Neonatal Network (CNN) and the Canadian Neonatal Follow-Up Network (CNFUN). The study population included preterm infants of 22^0 weeks' gestation to 28^6 weeks' gestation admitted between January 1, 2010 and September 30, 2011 to neonatal intensive care units (NICUs) participating in CNN. Infants with major congenital or chromosomal anomalies and those who were not offered mechanical ventilation or intensive care because of planned palliative care were excluded. In the present study, we report a subset of infants admitted to CNN participating centers during the 2010 to 2013 period whose short-term outcomes were previously reported [4] and for whom follow-up outcomes were also available (period 2010-2011).

1.2. Ethics

For CNN and CNFUN, primary data collection was approved by each institution's respective research ethics board or institutional quality improvement committee, as appropriate. The retrospective secondary analyses from the CNN and CNFUN databases for this study were approved by the Research Ethics Board of Mount Sinai Hospital and the Executive Committee of CNN and CNFUN. Data on neurodevelopmental outcomes were collected during follow-up visits at between 18 and 30 months' corrected age.

1.3. Source for data collection

Data on individual infants were collected as part of the ongoing CNN data collection system. All neonatal follow-up programs participated in CNFUN and collected data from the 28 of 30 level 3 NICUs units in Canada with a follow-up program during the study period from January 2010 to September 2011. At all affiliated sites, demographic and outcome data were collected from patient charts by trained research assistants using a computerized data entry program according to standardized outcome definitions [11]. The CNN database has been reported to have very high reproducibility and internal consistency [12].

1.4. Exposure groups:

Neonates were classified into the following 4 exposure groups:

- Group A: Neonates who were diagnosed with focal SIP. Focal SIP was diagnosed based on radiological finding of intestinal perforation; absence of radiological features of intestinal ischemia, such as fixed dilated bowel loops; absence of pneumatosis intestinalis, intraoperative surgical report indicating SIP; or histopathological confirmation of perforation located in the ileum and on the antimesenteric border.
- Group B: Neonates who were diagnosed with non-perforated NEC defined according to Bell's [13] staging as stage II.
- Group C: Neonates who were diagnosed with perforated NEC defined according to Bell's staging [13] as stage III and confirmed with radiological features, intraoperative diagnosis, or histological examination.
- Group D: Neonates who were not diagnosed with SIP or NEC.

1.5. Follow-up assessments

At 18 to 30 months' corrected age, each child was assessed at a CNFUN site by an experienced clinician whenever possible. Assessments by community health care professionals were used for 6% of the children. Caregiver socio-demographic and education information were obtained at the follow-up visit. The evaluation included a standardized history, physical and neurological examinations, and administration of the Bayley Scales of Infant and Toddler Development – third Edition (Bayley-III) assessment by a trained assessor [14]. Composite cognitive, language, and motor scores were obtained using the Bayley-III. In cases where the child could not be tested, the Bayley-III Adaptive Behavior questionnaires were administered. A diagnosis of cerebral palsy (CP) was made using standard definitions [15], and if present, the degree of functional impairment was classified using the Gross Motor Function Classification System (GMFCS) [16]. Hearing assessment results and the need for hearing aids or cochlear implants were obtained through the patient history. Ophthalmological follow-up results for retinopathy of prematurity (ROP) and visual status were documented. If vision history was unknown, visual impairment was defined as a small-scarred eye, sustained sensory nystagmus, or lack of response to a 1 cm object on a white background from a 30 cm distance.

1.6. Definitions of other variables

Gestational age was estimated using a hierarchy of in vitro fertilization date, last menstrual date, early antenatal ultrasound dating, obstetric estimate, and neonatal estimate, in that sequence. Small for gestational age was defined by birth weight below the 10^{th} percentile for an infant's gestational age and sex. Prenatal steroid use was defined as any corticosteroid administration before birth and classified as complete, partial, or none. Bronchopulmonary dysplasia (BPD) was defined as the need for oxygen at 36 weeks' postmenstrual age at NICU discharge or transfer [17]. Nosocomial sepsis was defined as the presence of a pathogenic organism in the blood or cerebrospinal fluid of a symptomatic infant after 2 days of age. Severe retinopathy was defined as retinopathy in either eye of stage 3 or higher [18].

1.7. Outcomes

The primary outcome was a composite outcome of death or significant neurodevelopmental impairment (NDI) (sNDI) at 18 to 30 months'

corrected age. A sNDI was defined as CP with GMFCS ≥III; Bayley-III motor, language, cognitive, or general adaptive composite scores of <70; the need for hearing aids or cochlear implant; bilateral visual impairment; or severe developmental delay that precluded Bayley-III assessment. Any NDI was defined as CP with GMFCS score >I, Bayley-III component score of <85, sensorineural or mixed hearing loss, or unilateral or bilateral visual impairment. Any NDI included infants with sNDI. The secondary outcomes were death; sNDI; NDI; the Bayley-III composite motor; language; cognitive and general adaptive scores; and weight (kg), length (cm), and head circumference (cm) at 18 to 30 months' corrected age.

1.8. Statistical analysis

Maternal details, infant characteristics, primary outcome, and secondary outcomes were compared for the 4 exposure groups using the Pearson Chi-square test for categorical variables and Student's *t* test or Wilcoxon rank test for parametric and nonparametric continuous variables, as appropriate. Univariate and multivariable logistic analyses were applied for primary and secondary outcomes. The following group comparisons were made: focal/SIP vs NEC with perforation; focal/SIP vs NEC (with or without perforation); focal/SIP vs no NEC, no perforation; all perforation vs NEC without perforation; all perforation vs no NEC, no perforation; and all NEC vs no NEC, no perforation. For multivariable analysis, the model was adjusted for gestational age, small for gestational age, prenatal steroids, caesarean section, multiple gestations, and SNAP-II score (Score for Neonatal Acute Physiology Version II). Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were estimated. All analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC) with a two-sided significance level of 0.05. We did not adjust p values for multiple comparisons.

2. Results

A total of 2,750 preterm infants with gestational age at birth between 22^{+0} and 28^{+6} weeks were admitted during the study period. After excluding 731 patients who did not fulfill the inclusion criteria – including 507 patients (18.4%) with no follow-up assessment – there were 2,019 patients who met the eligibility criteria. Of these, 39 (1.9%) infants had SIP/focal perforation, 61 (3%) had perforated NEC, 115 (5.7%) had non-perforated NEC, and 1,804 (89.4%) had none of these diagnoses. The distribution of included infants is presented in Fig. 1. The maternal and neonatal characteristics and neonatal outcomes are reported in Table 1. Neonates who had SIP or NEC were of relatively younger gestational ages and lower birth weights than those who did not. In unadjusted analyses, neonates with SIP had higher rates of neonatal morbidities compared to neonates with no NEC or SIP. Neonates with NEC also had higher rates of BPD, severe ROP, and infection (Table 1).

Before adjustment, the combined outcome of death or sNDI was more frequent in patients with NEC, SIP, or any perforation compared to infants with no SIP and no NEC. The majority of the unadjusted difference stemmed from higher mortality in neonates with SIP or NEC compared to those without SIP or NEC. Average Bayley-III motor, cognitive, and language composite scores were also lower in neonates with SIP or NEC compared to those without SIP or NEC (Table 2).

After multivariable adjustment, the odds of death or sNDI in patients with SIP, NEC, or all perforations were significantly higher compared to those in patients with no SIP and no NEC; however, there was no differences between SIP and perforated NEC patients or between SIP and all NEC patients. The majority of the difference was due to higher mortality, as there was no difference in sNDI among survivors (Table 3).

There were no differences regarding any growth outcomes among the groups, with one exception: smaller head circumference at 18-30 months' corrected age in infants who had bowel perforation or NEC compared to those with no SIP or NEC (Table 2). These differences persisted after adjustment for potential confounders (Table 3).

3. Discussion

In this large, national, multicentre, population-based cohort study we report the follow-up outcomes of a subset of patients included in our previous study for whom these data were available [4]. We identified that neonates with SIP or NEC had higher odds of death or significant NDI at 18 to 30 months compared to neonates without these conditions. The major contribution to these higher odds was higher mortality. Among survivors, Bayley-III cognitive, motor, and language

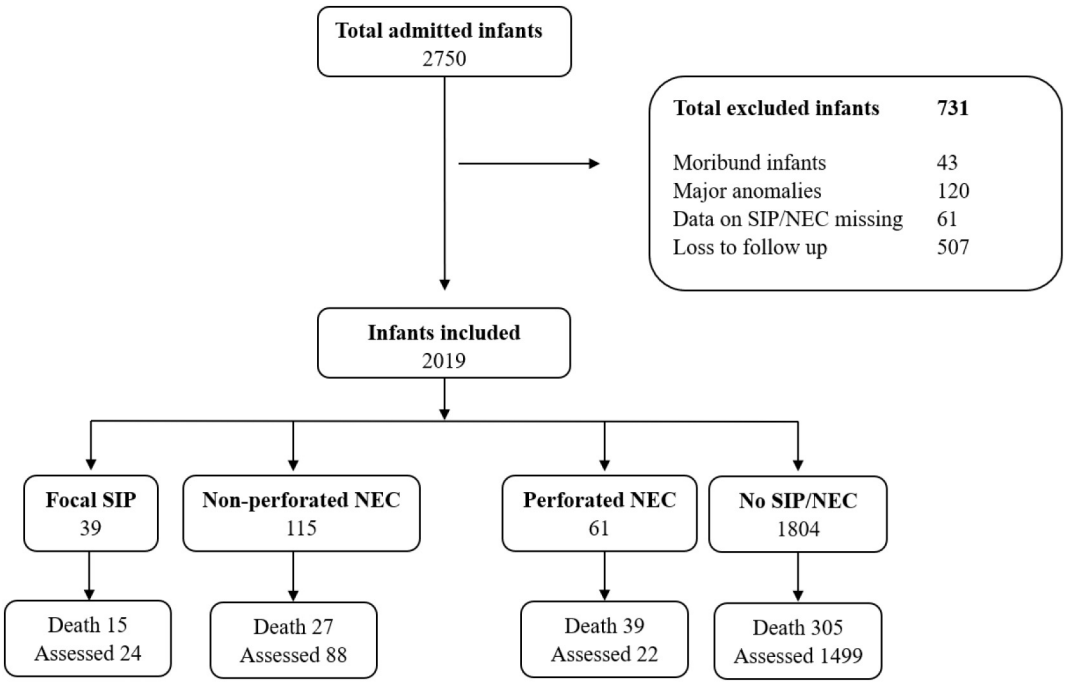

Fig. 1. Flow diagram of the study population.

Table 1
Maternal and infant characteristics and neonatal outcomes of the study population.

Characteristics	Focal/SIP (A)	NEC with perforation (B)	NEC, no perforation (C)	No NEC, no perforation (D)	p Values					
	n = 39	n = 61	n = 115	n = 1804	A vs B	A vs B+C	A vs D	A+B vs C	A+B vs D	B+C vs D
Maternal age, years	31.1 (6.0)	28.7 (6.2)	30.9 (5.7)	30.6 (5.9)	ns	ns	ns	ns	ns	ns
Smoking, n (%)	7 (18.0)	10 (16.4)	16 (13.9)	238 (13.2)	ns	ns	ns	ns	ns	ns
Antenatal steroid, n (%)	28 (77.8)	52 (86.7)	102 (90.3)	1548 (88.0)	ns	ns	ns	ns	ns	ns
Caesarean section, n (%)	22 (56.4)	25 (41.7)	67 (58.3)	1019 (56.7)	ns	ns	ns	ns	ns	ns
Gestational age, weeks	25.4 (1.5)	25.4 (1.7)	25.8 (1.4)	26.1 (1.5)	ns	ns	<**0.01**	ns	<**0.01**	<**0.01**
Birth weight, g	821 (182)	862 (229)	871 (238)	909 (241)	ns	ns	**0.01**	ns	**0.01**	**0.03**
Small for gestational age, n (%)	NR	NR	10 (8.7)	151 (8.4)	ns	ns	ns	ns	ns	ns
Male, n (%)	22 (56.4)	44 (72.1)	70 (60.9)	946 (52.5)	ns	ns	ns	ns	**0.01**	<**0.01**
Outborn, n (%)	9 (23.1)	9 (14.8)	17 (14.8)	275 (15.2)	ns	ns	ns	ns	ns	ns
Multiple gestations, n (%)	13 (33.3)	20 (32.8)	25 (21.7)	491 (27.2)	ns	ns	ns	ns	ns	ns
SNAP-II score >20, n (%)	17 (43.6)	29 (47.5)	47 (40.9)	567 (32.0)	ns	ns	ns	ns	<**0.01**	<**0.01**
Prophylactic indomethacin, n (%)	5 (12.8)	5 (8.2)	8 (7.0)	72 (4.0)	ns	ns	**0.02**	ns	**0.01**	**0.03**
Therapeutic indomethacin or ibuprofen, n (%)	21 (53.9)	30 (49.2)	60 (52.2)	749 (41.5)	ns	ns	ns	ns	ns	**0.01**
Grade 3/4 IVH, n (%)	13 (34.2)	12 (19.7)	17 (14.9)	259 (15.0)	ns	**0.01**	<**0.01**	ns	**0.01**	ns
BPD, n (%)	20 (76.9)	20 (62.5)	51 (52.6)	690 (45.4)	ns	**0.04**	<**0.01**	**0.04**	<**0.01**	**0.03**
Severe ROP, n (%)	7 (28.0)	7 (23.3)	28 (30.4)	167 (13.8)	ns	ns	**0.04**	ns	**0.02**	<**0.01**
Nosocomial infection, n (%)	22 (56.4)	35 (57.4)	58 (50.4)	429 (23.8)	ns	ns	<**0.01**	ns	<**0.01**	<**0.01**

Data are expressed as mean (standard deviation) or number (%) as appropriate. Comparisons between groups were done using the Pearson chi-square test for categorical variables and the Student's t-test or Wilcoxon rank test for parametric and nonparametric continuous variables, as indicated.
Abbreviations: BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NR, not reported (due to cell size <5 according to network policy); ns, statistically non-significant; ROP, retinopathy of prematurity; SIP, spontaneous intestinal perforation; SNAP-II, Score for Neonatal Acute Physiology Version II.
Bold text indicates p<0.05.

composite scores were lower in neonates who had SIP or NEC; however, after adjustment, only motor and cognitive scores were lower – and only among neonates with NEC.

Data on the neurodevelopment of infants with SIP are limited in the literature [7,8,19,20]. In a cohort of extremely low birth weight (ELBW) (<1000 g) infants (n = 11,960; SIP incidence 2.3%), Wadhawan et al. reported a higher adjusted risk of NDI (adjusted OR 2.17, 95% CI 1.4–3) and composite of death or NDI (adjusted OR 2.21, 95% CI 1.5–3.2) in patients with SIP [8] compared to those without SIP. Using data from the same database, Shah et al. reported lower Bayley Scales of Infant Development-II scores, after adjustment, among infants with SIP compared to those without SIP or NEC – both for the mental development (mean 68.2, 95% CI 60.2-76.2 vs 87.1, 95% CI 85.8-88.4, p<0.001) and for the psychomotor development (mean 73.4, 95% CI 65.9-80.9 vs 91.2, 95% CI 90.0-92.5, p<0.001) indices. They also did not identify any differences in neurodevelopmental outcomes between SIP patients and surgically treated NEC patients (mean mental development index 68.2, 95% CI 60.2-76.2 vs 78.1, 95% CI 71.4-84.8, p = 0.29; and mean

Table 2
Unadjusted comparisons of outcomes between groups.

Outcomes	Focal/SIP (A) n = 39	NEC with perforation (B) n = 61	NEC, no perforation (C) n = 115	No NEC, no perforation (D) n = 1804	p Values					
					A vs B	A vs B+C	A vs D	A+B vs C	A+B vs D	B+C vs D
Primary outcome										
Death or significant NDI at 18-30 months' CA, n (%)	21 (53.9)	45 (73.8)	51 (44.4)	544 (30.2)	**0.04**	ns	<**0.01**	<**0.01**	<**0.01**	<**0.01**
Secondary outcomes										
Death, n (%)	15 (38.5)	39 (63.9)	27 (23.5)	305 (16.9)	**0.01**	ns	<**0.01**	<**0.01**	<**0.01**	<**0.01**
Significant NDI, n (%)	6 (25.0)	6 (27.3)	24 (27.3)	239 (16.0)	ns	ns	ns	ns	ns	<**0.01**
NDI, n (%)	16 (66.7)	12 (54.6)	56 (63.6)	662 (44.3)	ns	ns	**0.03**	ns	**0.03**	<**0.01**
BSID-III										
Motor score, median (IQR)	90 (85,100)	100 (90, 105)	90 (80, 100)	95 (90, 105)	ns	ns	**0.01**	ns	ns	**0.01**
Language score, median (IQR)	79 (74, 94)	89 (79, 100)	86 (74, 94)	91 (79, 100)	ns	ns	**0.03**	ns	ns	<**0.01**
Cognitive / general score, median (IQR)	90 (70, 97)	91 (88, 94)	90 (79, 97)	94 (85, 100)	ns	ns	**0.03**	ns	**0.01**	<**0.01**
Growth										
Weight (g) at 18-30 months' CA	10,721 (1,401)	10,276 (1,258)	10,924 (1,799)	10,781 (1,577)	ns	ns	ns	ns	ns	ns
Length (cm) at 18-30 months' CA	80.0 (4.1)	80.3 (3.4)	80.2 (3.9)	80.9 (4.1)	ns	ns	ns	ns	ns	ns
Head circumference (cm) at 18-30 months' CA	46.6 (1.4)	46.5 (1.4)	46.7 (2.1)	47.3 (1.9)	ns	ns	ns	ns	<**0.01**	<**0.01**
Other outcomes										
Rehospitalizations, including need for surgery, n (%)	9 (37.5)	14 (63.6)	46 (53.5)	509 (34.7)	ns	ns	ns	ns	**0.03**	<**0.01**

Data are presented as median (IQR) or number (%) as appropriate. Comparisons between groups were done using the Pearson Chi-square test for categorical variables and the Student's *t*-test or Wilcoxon rank test for parametric and nonparametric continuous variables, as indicated. Abbreviations: BSID-III, Bayley Scales of Infant and Toddler Development – third edition; CA, corrected age; IQR, interquartile range; NDI, neurodevelopmental impairment; NEC, necrotizing enterocolitis; ns, statistically non-significant; SIP, spontaneous intestinal perforation.
Bold text indicates p<0.05.

Table 3
Adjusted comparisons of outcomes between groups.

	Focal/SIP (A) vs NEC with perforation (B)	Focal/SIP (A) vs NEC (with and without perforation) B+C	SIP (A) vs No NEC, no perforation (D)	All perforation (A+B) vs NEC without perforation (C)	All perforation (A+B) vs No NEC, no perforation (D)	All NEC (B+C) vs No NEC, no perforation (D)
Adjusted odds ratios (95% CI)						
Outcomes						
Primary outcome						
Death or significant NDI at 18-30 months' CA	0.44 (0.17, 1.17)	0.93 (0.42, 2.03)	**2.11 (1.01, 4.42)**	**2.32 (1.25, 4.28)**	**3.97 (2.43, 6.48)**	**2.58 (1.81, 3.68)**
Secondary outcomes						
Death	**0.28 (0.10, 0.78)**	0.97 (0.44, 2.12)	**2.43 (1.11, 5.32)**	**3.41 (1.84, 6.32)**	**5.87 (3.54, 9.74)**	**2.95 (2.01, 4.35)**
Significant NDI	1.09 (0.27, 4.63)	1.07 (0.36, 3.18)	1.60 (0.60, 4.27)	1.16 (0.48, 2.81)	1.65 (0.82, 3.34)	1.58 (0.99, 2.52)
NDI	1.45 (0.36, 5.89)	1.06 (0.39, 2.91)	2.00 (0.81, 4.91)	0.87 (0.39, 1.92)	1.64 (0.88, 3.07)	**1.77 (1.17, 2.67)**
Other outcomes						
Rehospitalizations, including need for surgery	**0.16 (0.03, 0.78)**	0.39 (0.14, 1.08)	0.92 (0.38, 2.26)	0.97 (0.45, 2.08)	1.68 (0.91, 3.11)	**1.97 (1.31, 2.96)**
Adjusted β-coefficients (95% CI)						
BSID-III						
Motor score	-0.99 (-8.75, 6.76)	0.18 (-6.91, 7.28)	-3.52 (-9.81, 2.78)	0.25 (-5.59, 6.09)	-3.46 (-8.13, 1.21)	**-4.37 (-7.41, -1.33)**
Language score	-3.00 (-10.4, 4.36)	-2.97 (-10.3, 4.40)	-6.49 (-14.0, 1.04)	-0.39 (-6.40, 5.62)	-3.98 (-9.50, 1.54)	-3.21 (-6.73, 0.30)
Cognitive / general score	-5.56 (-13.1, 1.95)	-1.61 (-9.29, 6.07)	-5.01 (-11.3, 1.33)	1.35 (-4.88, 7.58)	-2.66 (-7.30, 1.98)	**-3.90 (-6.89, -0.90)**
Growth						
Weight (g) at 18-30 months' CA	565 (-144, 1275)	-7 (-707, 694)	69 (-554, 691)	-393 (-953, 167)	-206 (-654, 242)	68 (-231, 367)
Length (cm) at 18-30 months' CA	-0.26 (-2.46, 1.95)	0.02 (-1.64, 1.69)	-0.36 (-2.02, 1.31)	0.12 (-1.23, 1.47)	-0.45 (-1.67, 0.76)	-0.55 (-1.34, 0.24)
Head circumference (cm) at 18-30 months' CA	0.42 (-0.30, 1.14)	0.16 (-0.66, 0.97)	-0.42 (-1.15, 0.31)	-0.09 (-0.74, 0.56)	**-0.61 (-1.13, -0.09)**	**-0.56 (-0.91, -0.22)**

Data are differences (95% confidence intervals) between compared groups yielded by logistic regression models adjusted for gestational age, small for gestational age, prenatal steroids, caesarean section, multiple gestations, and SNAP-II score (Score for Neonatal Acute Physiology Version II).
Abbreviations: BSID-III, Bayley Scales of Infant and Toddler Development – third edition; CA, corrected age; CI, confidence interval; NDI, neurodevelopmental impairment; NEC, necrotizing enterocolitis; SIP, spontaneous intestinal perforation.
Bold text indicates statistically significant results.

psychomotor development index 73.4, 95% CI 65.9-80.9 vs 80.1, 95% CI 73.7, 86.4, p = 0.72) [20]. Neurodevelopmental outcomes of infants with NEC have been extensively reported in the literature [21]. Two meta-analyses reported that preterm infants with NEC had higher odds of CP and motor, cognitive, and visual impairment compared to those without NEC [10,22]. Both meta-analyses included studies using the BSID versions I-II and other scales, but not the most recent Bayley-III, for which there are few data in the literature regarding NEC patients. The previous meta-analyses reported data from observational studies, mostly from the 1990s to the early 2000s. In this report we identified that infants with SIP and NEC were associated with death or NDI, and thus, new therapies specifically aiming to prevent NEC and SIP and improve long-term outcomes in survivors with NEC and SIP are urgently needed [23].

Several factors could explain our findings of an association with death or neurodevelopmental outcomes in infants with medically or surgically treated NEC or SIP. Inflammation that develops after perforation or after ischemia/necrosis lead to white matter injury, which explains most of the neurological impairment in preterm infants [24,25]. Systemic inflammation is usually associated with NEC [26], which is, in essence, a bowel inflammatory disease in which circulating cytokines are known to be elevated. Lodha et al. reported a trend for a relationship between higher cytokine levels and worse neurodevelopment in patients with NEC [27]. Another source of inflammation is sepsis, which is frequently associated with NEC. Sepsis is independently associated with NDI in preterm infants [28]. Martin et al. showed that neurodevelopment among surviving NEC patients were poorer if they also had sepsis [29]. Systemic inflammation is not commonly reported in infants with SIP [3], but associated peritonitis is a risk in the event of perforation [30]. Additionally, neonates with NEC can go into a phase of shock and subsequent brain hypoperfusion. Finally, it has been reported that more than half of infants with NEC or SIP undergoing a laparotomy may have a loss of cerebrovascular autoregulation during the intervention [31]. Infants with surgically treated NEC or SIP had more severe brain damage according to MRI scores than those with medical NEC [32]. However, it is difficult to distinguish impact of surgery as a cause and effect as patients who required surgery had a higher severity of illness. Also, the type of surgical intervention (primary laparotomy vs drainage) might impact mortality and neurodevelopment. In patients with perforated NEC, a clinical trial showed no differences in mortality at 90 days between the options [33], whereas another study including perforated patients with both NEC and SIP did not find any differences in mortality at 6 months [34]. Two cohort studies also showed no differences in short-term mortality in patients with SIP regarding the primary treatment [35,36]. Regarding neurodevelopment, a large prospective cohort study showed that, in patients with either NEC or SIP, primary peritoneal drainage was associated with higher mortality or NDI at 18 months than primary laparotomy, which disappeared after adjustment for potential confounders [37]. The forthcoming results of the recently finalized NEST trial will help to clarify the best surgical option regarding mid-term outcome in patients with NEC [38]. Data on SIP neurodevelopment outcomes depending on the primary surgical treatment were not reported in previous studies [8,19,20].

Necrotizing enterocolitis has been previously associated with poor weight gain and linear and head growth during the first neonatal admission [39]. However, in the current study we did not identify any differences in weight and length at 18 months' corrected age after

adjustment. On the other hand, we identified that children who had NEC and those who had any perforation had smaller head circumferences than those with no NEC and no SIP. Hong et al. reported no differences in the proportions of patients with weight, length, or head circumference below the 3rd percentile at 18 to 30 months' corrected age when comparing infants with no NEC, NEC treated medically, and NEC requiring surgical intervention, despite the fact that proportions were different at discharge [40]. Dilli et al. similarly did not report any differences in body weight, body length, and head circumference between infants with NEC and no NEC at the same corrected age [41]. Reasons that could explain growth impairment in this population include prenatal factors like a history of intrauterine growth restriction, perinatal inflammation, catabolic state, and malabsorption. Short bowel syndrome is a known complication after surgical NEC. Cole et al. reported that infants with short bowel syndrome had more weight-, length-, and head circumference-related growth impairment than infants with surgical NEC without short bowel syndrome, medical NEC, or no NEC [42]. Adesanya et al. reported no differences between SIP and NEC infants, although they made no comparison between SIP survivors and other ex-preterm infants [19]. Shah et al. reported no differences in weight and head circumference, between NEC and infants without NEC or SIP; medical and surgical NEC; SIP and infants without NEC or SIP; and surgical NEC and SIP, at 18 months' corrected age [20]. Thus, the literature regarding growth outcomes following gastrointestinal emergencies during the neonatal period is limited; however, it points towards the possibility of growth impairments and suggests careful vigilance in the follow-up of these children.

Of note, the mortality odds were different from no NEC and no SIP cohort in the majority of our adjusted comparisons. We chose a composite primary outcome for this study because mortality and neurodevelopment are competitive outcomes. We speculate that the most severe cases would probably experience more severe NDI and higher mortality at the same time. This could explain the absence of adjusted differences in sNDI while the adjusted mortality was higher for SIP, perforated, and NEC infants. We adjusted our models for potential perinatal confounding factors of death or mortality identified based on the literature. These included gestational age [43], multiple births [44], antenatal steroids [45], small for gestational age [46], mode of delivery [47], clinical severity measured by the SNAP-II score at 12 hours of life [48], and intraventricular hemorrhage (IVH) grades 3/4. IVH, especially grades 3 and 4, is associated with death and impaired neurodevelopment in preterm infants [49]. In our cohort, the group of patients with SIP had higher rates of grades 3/4 IVH than those without NEC or SIP, and also compared to patients with NEC. Unfortunately, the age at diagnosis of SIP, NEC, or IVH was not recorded in the database. Thus, no temporal associations could be established. However, it is likely that, in patients with NEC, IVH preceded the diagnosis, whereas in the case of SIP it is difficult to ascertain timing.

Our study has several strengths, including a multicentre design and the inclusion of a relatively large, population-wide cohort with standardized assessments. However, there are also limitations. Despite accessing a national cohort, we still had a relatively small number of patients with SIP, which could have limited the conclusions concerning this group of patients. Further, most of patients with SIP had the diagnosis confirmed in the operating room after a laparotomy, but in those patients who underwent peritoneal drainage as the only treatment, the diagnosis was based only on clinical and radiological signs. Additionally, though we adjusted for confounders in our analyses, residual confounding (e.g., due to lack of data on kind of surgical treatment) cannot be ruled out and some patients (18.4%) were lost to follow-up. Finally, data on longer-term outcomes (e.g., at school age) were not available.

4. Conclusions

Infants with SIP, NEC, or any bowel perforation (either in the context of SIP or NEC) had higher odds of death or sNDI at 18-30 months' corrected age compared to infants with no NEC and no SIP. Patients with any perforation also had higher odds of death or sNDI compared to infants with non-perforated NEC. Head circumferences were smaller in infants who had NEC or any bowel perforation compared to those without NEC or SIP. Further investigations regarding the neuroprotection of neonates with gastrointestinal complications are needed.

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