



Mortality associated with laparotomy-confirmed neonatal spontaneous intestinal perforation: A prospective 5-year multicenter analysis



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ABSTRACT

Background: Spontaneous intestinal perforation (SIP) has been recognized as a distinct disease entity. This study sought to quantify mortality associated with laparotomy-confirmed SIP and to compare it to mortality of laparotomy-confirmed necrotizing enterocolitis (NEC).

Methods: Data were prospectively collected on 177,618 very-low-birth-weight (VLBW, 401–1500 g) neonates born between January 2006 and December 2010 admitted to US hospitals participating in the Vermont Oxford Network (VON). SIP was defined at laparotomy as a focal perforation of the intestine without features suggestive of NEC or other intestinal abnormalities. The primary outcome was in-hospital mortality.

Results: At laparotomy, 2036 (1.1%) neonates were diagnosed with SIP and 4076 (2.3%) with NEC. Neonates with laparotomy-confirmed SIP had higher mortality (19%) than infants without NEC or SIP (5%, $P = 0.003$). However, laparotomy-confirmed SIP patients had significantly lower mortality than those with confirmed NEC (38%, $P < 0.0001$). Mortality in both NEC and SIP groups decreased with increasing birth weight and mortality was significantly higher for NEC than SIP in each birth weight category. Indomethacin and steroid exposure were more frequent in the SIP cohort than the other two groups ($P < 0.001$).

Conclusions: In VLBW infants, the presence of laparotomy-confirmed SIP increases mortality significantly. However, laparotomy-confirmed NEC mortality was double that of SIP. This relationship is evident regardless of birth weight. The variant mortality of laparotomy-confirmed SIP versus laparotomy-confirmed NEC highlights the importance of differentiating between these two diseases both for clinical and research purposes.

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Necrotizing enterocolitis (NEC) is the most common abdominal surgical emergency in neonates. At laparotomy for suspected NEC, the surgeon may find any degree of disease from healthy bowel to complete infarction of intestine. Spontaneous intestinal perforation (SIP) is an isolated, focal intestinal perforation with otherwise normal appearing surrounding tissue [1,2]. Once thought to be a variant of necrotizing enterocolitis (NEC) [3–5], SIP is now generally considered a distinct clinical entity [2,6–10].

In addition to the surgical findings, SIP appears to have variant clinical features and outcomes from NEC. Clinically, both affect a similar patient population: premature neonates. However, patients with SIP tend to have lower birth weights and may be less likely to develop severe illness in the form of hypotension, metabolic acidosis, hyponatremia, neutropenia, and thrombocytopenia [11,12]. Whereas

plain films in perforated NEC often show intraperitoneal free air and pneumatosis intestinalis, the latter is typically absent in SIP. Despite these differences, the diagnosis may be unclear until a laparotomy is performed and the tissue is directly seen.

Reports involving small numbers of patients suggest that SIP may have a better prognosis than NEC [7], however, no large-scale quantitative studies have been published, leaving the surgeon faced with a finding of SIP at laparotomy unable to accurately predict the patient's outcome. In this investigation, using a nationwide cohort of neonates, we sought to quantify the comparative mortalities of laparotomy-confirmed SIP and NEC.

1. Methods

The Vermont Oxford Network (VON) [13] is a nonprofit voluntary collaboration that prospectively collects data on infants of birth weight 401–1500 g who are born at participating institutions or who are transferred to such an institution within 28 days of birth. These data are accrued until neonates are discharged from the hospital, die, or reach 1 year of age in hospital. Data are collected by local staff using

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uniform definitions and then submitted to the VON central office. Records are subjected to automated checks and returned for correction if needed. This study was performed as part of an ongoing collaboration between VON and a group of pediatric surgeons. Compilation and quality review of data were performed with surgical input, ensuring that data fields were completed and that any ambiguities in the entries were clarified. VON is approved by the University of Vermont Institutional Review Board (#04-370) and exempted from review at Boston Children's Hospital.

Among the 655 US VON centers, survey data indicate that 83% had a pediatric surgeon on site or at a closely related institution and 81% had a pediatric anesthesiologist on site or at a closely related institution. Thirty-seven percent of centers were classified as having a type A NICU (restriction on assisted ventilation or only perform minor surgery). Forty-seven percent had a type B NICU (no restriction on assisted ventilation and perform major surgery, i.e. repair of TEF/esophageal atresia, or meningomyelocele). The remaining 16% of centers had a type C NICU (no restriction on ventilation and perform cardiac surgery requiring bypass for neonates).

For this cohort study, data were prospectively collected in the VON database from United States centers between January 2006 and December 2010 on newborns weighing between 401 and 1500 g. Neonates with major birth defects, as listed in the VON Manual of Operations [14] (i.e. anencephaly, holoprosencephaly, and major cardiac defects) and those with a length of stay 3 or fewer days were excluded.

Only patients whose bowel was seen directly at laparotomy were included in the NEC and SIP groups in the primary analysis. The VON Manual of Operations considers SIP and NEC as distinct diagnoses. In contradistinction to NEC, SIP is defined as a diagnosis made by the surgeon that demonstrates a single focal intestinal perforation with the remainder of the bowel appearing normal. SIP and NEC could occur in the same patient at different times and thus a patient could legitimately carry both codes in the database.

The VON database was queried for the presence of a surgical code and the diagnosis of SIP or NEC specifically to exclude those who were given a diagnosis on clinical and radiographic parameters alone. Neonates treated medically (7877) or with peritoneal drainage alone (1190), in whom, by VON definition SIP or NEC could not be differentiated, were excluded from the primary analysis.

Statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC). The primary outcome was mortality prior to 1 year of age or hospital discharge. Multivariate logistic regression modeling was performed with adjustments for clustering of infants within hospitals [generalized estimating equations (GEE) were used to account for correlation between infants at a given hospital]. Model covariates included gestational age, small for gestational age, maternal race, gender, multiple births, Apgar score at 1 minute, birth location, vaginal delivery, and antenatal steroid exposure. Adjusted odds ratios for mortality were calculated to compare laparotomy-confirmed SIP to laparotomy-confirmed NEC. A second comparison was then made to compare the mortality of SIP to the baseline or control cohort, defined as VLBW infants with neither NEC nor SIP. P values <0.05 were considered significant. Categorical measures of patient and obstetric characteristics (Table 1) and comorbidities and exposures (Table 3) were compared using z-tests and continuous measures were assessed by unpaired Student's t-test.

2. Results

There were 177,618 neonates that met the inclusion criteria for one of the three arms of this study. Of these, 2036 patients had laparotomy-confirmed SIP (incidence 1.1%), 4076 had laparotomy-confirmed NEC (2.3%, *P* versus SI: *P* < 0.0001), and 171,506 had neither SIP nor NEC (baseline cohort).

Table 1
Demographic and obstetric characteristics.

Measure	Baseline (no NEC, no SIP; <i>n</i> = 171,506)	Laparotomy-confirmed SIP (<i>n</i> = 2036)	Laparotomy-confirmed NEC (<i>n</i> = 4076)	<i>P</i> -value (SIP vs. NEC)
Sex (% male)	49.4	61.9	57.9	0.003
Birth weight (mean ± SD)	1,079.9 ± 281.3	812.9 ± 231.1	892.1 ± 260.6	<0.001
Gestational age (mean ± SD)	28.4 ± 2.8	25.6 ± 2.2	26.5 ± 2.3	<0.001
Small for gestational age (%)	20.2	9.1	11.8	<0.001
Birth location (% outborn)	15.0	36.0	34.1	0.141
Vaginal delivery (% vaginal)	27.0	30.3	33.1	0.024
Multiple births (%)	28.1	27.3	23.1	<0.001
Apgar 1 (mean ± SD)	5.6 ± 2.4	4.3 ± 2.4	4.8 ± 2.4	<0.001
Apgar 5 (mean ± SD)	7.5 ± 1.7	6.5 ± 2.0	7.0 ± 1.9	<0.001

NEC = necrotizing enterocolitis, SIP = spontaneous intestinal perforation.

Patient and obstetric characteristics are listed in Table 1. There were small but significant differences between the SIP and NEC groups. Notably, the SIP patients had lower birth weights and gestational ages, were more likely to be male, and had lower Apgar scores.

The mortality of laparotomy-confirmed SIP was 19% versus 5% in the control group (OR 1.24, 95% CI: 1.08–1.44; *P* = 0.003). Laparotomy-confirmed SIP mortality was significantly lower than confirmed NEC mortality; 19% versus 38% overall (OR 0.33, 95% CI: 0.28–0.37, *P* < 0.0001). Number and mortality per birth weight group for SIP, NEC, and baseline groups are shown in Table 2. Fig. 1 shows mortality by birth weight category for laparotomy-confirmed SIP versus controls and adjusted odds ratios for mortality are listed for each category (SIP compared with control group). In the lowest birth weight category (401–500 g), SIP mortality was lower than that of baseline infants. It was significantly higher than baseline between 751–1000 g and 1251–1500 g. Fig. 2 compares laparotomy-confirmed SIP to NEC by birth weight category with adjusted odds ratios for mortality. In each category, SIP mortality was less than NEC mortality (*P* < 0.0001).

Comorbid conditions and exposures are shown in Table 3. The following were more frequently seen in the laparotomy-confirmed SIP group than the confirmed NEC or baseline groups (*P* < 0.05): presence of a patent ductus arteriosus, intraventricular hemorrhage, fungal infection, exposure to steroids for chronic lung disease, and indomethacin administration.

A total of 9067 patients had either NEC or SIP codes but did not undergo laparotomy: 7,877 (87%) were treated medically with 20%

Table 2
Mortality by diagnosis and birth weight.

	Laparotomy-confirmed SIP		Laparotomy-confirmed NEC		Baseline (no NEC, no SIP)	
	<i>n</i>	Mortality %	<i>n</i>	Mortality %	<i>n</i>	Mortality %
401–500	84	31	124	62	2558	43
501–750	907	26	1343	42	25,376	20
751–1000	633	14	1315	37	38,464	5
1001–1250	284	4	808	35	46,522	2
1251–1500	127	10	482	32	58,539	1
Overall	2035	19	4072	38	171,459	5

NEC = necrotizing enterocolitis, SIP = spontaneous intestinal perforation.

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