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Morbidity and mortality among "big" babies who develop necrotizing enterocolitis: A prospective multicenter cohort analysis

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ABSTRACT

Background: Necrotizing enterocolitis (NEC) is classically a disease of prematurity, with less reported regarding morbidity and mortality of this disease among other infants.
Methods: Data were prospectively collected from 2009 to 2015 at 252 Vermont Oxford Network member centers on neonates with birth weight > 2500 g admitted to a participating NICU within 28 days of birth.
Results: Of 1629 neonates with NEC, gestational age was 37 (36, 39) weeks, and 45% had major congenital anomalies, most commonly gastrointestinal defects (20%), congenital heart defects (18%), and chromosomal anomalies (7%). For the 23% of infants who had surgery for NEC, mortality and length of stay were 23% and 63 (36, 94) days versus 8% and 34 (22, 61) days in medical NEC. Independent predictors of mortality were congenital heart defects ($p < 0.0001$), chromosomal abnormalities ($p < 0.05$), other congenital malformations ($p < 0.001$), surgical NEC ($p < 0.0001$), and sepsis ($p < 0.05$). All of these in addition to gastrointestinal defects were independent predictors of increased length of stay. Nutritional morbidity at discharge included 6% receiving no enteral feeds and 27% who were <10th percentile weight-for-age.
Conclusions: Major congenital anomalies are present in nearly half of >2500 g birth weight infants diagnosed with necrotizing enterocolitis. Morbidity and mortality increase with sepsis, surgical disease, and congenital anomalies.
Type of study: Prognosis Study.
Level of evidence: Level II.

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Necrotizing enterocolitis (NEC) is the most common surgical emergency in neonates and is classically a disease of prematurity [1], with approximately 90% of cases diagnosed in preterm infants [2]. Among these preterm infants, the incidence and mortality of NEC decrease with higher birth weights [3]. While NEC has been extensively described in preterm infants, less is known about the heterogeneous group of normal birth weight infants who are diagnosed with NEC. In full-term infants, NEC is often associated with comorbidities where factors such as asphyxia or metabolic abnormalities may be at play; for example, congenital heart disease is associated with increased risk for NEC in both VLBW and full-term infants [2,4]. We utilized a prospectively collected quality improvement database from a collaborative of neonatal intensive care units to: 1) obtain benchmark data on mortality and length of stay among neonates with birth weight > 2500 g who were diagnosed with NEC, 2) identify independent risk factors for these outcomes and 3) explore other potential morbidities in this patient population.

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1. Method

1.1. Study designs

Vermont Oxford Network (VON) is a nonprofit voluntary collaboration of health professionals dedicated to improving the care of high risk infants and their families (www.vtoxford.org). In support of this mission, VON maintains databases for use in quality improvement. Members may report data for VLBW infants only (defined as either a gestational age of 22 to 29 weeks or a birth weight of 401 to 1500 g) or report data for all NICU admissions regardless of birth weight or gestational age. Between 2009 and 2015, 1074 hospitals participated in VON with 489 reporting data on all NICU infants. Data are centrally collected and analyzed, and strict definitions are applied using a universal Manual of Operations.

Infants at participating North American centers diagnosed with NEC who had birth weights greater than 2500 g were included in this study. One Canadian center and 251 American centers contributed data for at least one included infant (Appendix 1; online only). Survival was defined as hospitalization at 1 year of age or discharge home without readmission.

Clinical diagnosis of NEC was defined by at least one physical finding (bilious gastric aspirate or emesis, abdominal distention, or occult/gross blood in the stool in the absence of anal fissures) *and* at least one radiographic finding (pneumatosis intestinalis, hepatobiliary gas, or pneumoperitoneum). NEC could also be diagnosed at laparotomy or at postmortem examination. For each infant diagnosed with NEC, type of surgery for NEC was recorded, if applicable. For each infant, all surgical procedures were reported from a list of defined procedures in the VON Manual of Operations [5].

Any major congenital anomalies, as defined by the VON Manual of Operations, were reported for each infant [5], with some infants having multiple anomalies. All reported anomalies not specifically defined by an available code were reviewed by surgeons and appropriately classified. Isolated atrial or ventricular septal defects were not included as serious congenital heart disease, as no data on clinical severity were collected.

Sepsis was defined by cerebral spinal fluid or blood culture positive for fungus or any of 30 defined bacterial pathogens. Cultures positive for coagulase negative staphylococcus were only included if the infant also had signs of generalized infection *and* underwent treatment with five or more days of intravenous antibiotics after the culture was obtained. Weight for age percentile was calculated using the Fenton growth standards for all infants discharged home at less than 50 weeks post menstrual age [6], and using the World Health Organization growth standards adjusted for gestational age for all infants discharged home at greater than 50 weeks post menstrual age [7]. Infants with a less than 15 day length of stay were not included in calculations of weight for age at discharge, so that physiological neonatal weight loss did not bias the results [8].

"Initial resuscitation" refers to interventions performed in the delivery room or in a resuscitation area immediately following birth and prior to NICU admission. Resuscitation strategies recorded include the use of supplemental oxygen, face mask ventilation, nasal continuous positive airway pressure (CPAP), endotracheal tube ventilation, the use of epinephrine, and cardiac compressions. Assisted ventilation was defined as intermittent positive pressure ventilation through an endotracheal tube with a conventional ventilator (intermittent mandatory ventilation rate < 240/min) at any time after leaving the initial resuscitation area. The number of days of assisted ventilation includes any complete or partial day during which the infant received ventilation via endotracheal intubation and a conventional ventilator.

This study was performed as part of an ongoing collaboration between VON and pediatric surgeons at Boston Children's Hospital. The Committee on Human Research at the University of Vermont approved the use of the Vermont Oxford Network Research Repository for this analysis (#15-143), and IRB exemption was granted at Boston Children's Hospital (IRB-P00002185).

1.2. Statistical methods

Multivariate logistic regression was used to assess risk factors for mortality and Poisson regression was used to assess risk factors for increased length of stay (LOS) among surviving infants, controlling for clustering of infants within hospitals. Models included all variables in Table 1; those with P-values <0.05 were considered independent predictors. All analyses were produced using SAS version 9.4 (SAS Institute, Cary, NC).

2. Results

There were 252 centers that contributed data on 1629 neonates >2500 g birth weight (60% male) who developed NEC. Median (IQR) gestational age in this cohort was 37 (36, 39) weeks (Table 1). Major congenital anomalies were seen in 44%, most commonly gastrointestinal defects (20%), congenital heart defects (18%), and chromosomal anomalies (7%); 10% had other congenital anomalies.

Of the 1629 included infants with NEC, 380 (23%) underwent surgery for NEC (surgical NEC), including 39 infants who received primary peritoneal drainage (PPD). Of the infants who received PPD, 30 also underwent laparotomy (with 7 deaths in this group), five died without further surgical intervention, and four survived to discharge without any additional abdominal surgeries. Mortality was 22% among infants with surgical NEC and 8% among infants with medical NEC (ARR 2.2 (1.7–2.9), with median (IQR) length of stay among survivors of 63 (36, 94) and 34 (22, 61) days, respectively ($p < 0.0001$). The proportion of infants with surgical NEC who had a major birth defect was 51% compared to 42% of those infants with medical NEC. Fig. 1 demonstrates prevalence and percent mortality of each significant independent predictor of death identified; the top of each gray bar indicates the proportion of infants in this study affected by each given risk factor, which ranged from 7% for chromosomal anomalies to 23% for surgical NEC. Infants who survived are represented by the light gray portion of the bar, and nonsurvivors are represented by the dark gray portion, with percent mortality for infants with each risk factor displayed.

Table 1
Patient characteristics, comparing infants with medical and surgical NEC.

	Medical NEC	Surgical NEC
Number of infants	1249	380
Birth Weight (g: median, Q1, Q3)	3035 (2754, 3453)	3010 (2739, 3405)
Gestational Age (weeks; median, Q1, Q3)	37 (36, 39)	37 (36, 39)
Apgar		
1 min (median, Q1, Q3)	8 (6, 8)	8 (5, 8)
5 min (median, Q1, Q3)	9 (8, 9)	9 (8, 9)
Male (%)	60	60
Maternal Hypertension (%)	15	21
Chorioamnionitis (%)	5	6
Small for Gestational Age (%)	8	10
Multiple Gestation (%)	4	2
Cesarean Delivery (%)	45	46
Outborn (%)	46	58
Major Birth Defect (%)	42	51
Any Initial Resuscitation (%)	52	50
Oxygen	49	48
Face mask	25	26
Intubation	13	18
CPAP	14	14
Sepsis (%)	14	27
Respiratory Distress Syndrome (%)	14	12
Assisted Ventilation (%)	59	97
Duration of Assisted Ventilation (median, Q1, Q3)	1 (0, 7)	7 (3, 18)
Any abdominal surgery (%)	35	100

NEC: necrotizing enterocolitis. CPAP: continuous positive airway pressure.

Overall mortality for NEC was 11% in this cohort, and 5% among infants without any major congenital anomaly. Significant independent predictors of mortality on multivariate logistic regression were congenital heart defects ($p < 0.0001$), chromosomal abnormalities ($p < 0.05$), other congenital malformations ($p < 0.001$), surgical NEC ($p < 0.0001$), and sepsis ($p < 0.05$) (Table 2). Risk factors for increased length of stay among survivors included the risk factors for mortality, listed above, and the presence of gastrointestinal defects ($p < 0.0001$) (Table 3).

In exploring additional outcomes, major nutritional morbidity was observed among survivors. Despite a low prevalence of small for gestational age infants, as would be expected in this cohort of infants selected by birth weight criteria, by the time of discharge the percent of infants who were less than the tenth percentile weight for age had increased (Table 4). At the time of discharge, 7% of the infants with medical NEC were receiving no enteral feeds, and 3% of those with surgical NEC were receiving no enteral feeds. During the initial hospital stay, 14% of infants underwent surgery for gastrostomy or jejunostomy tube placement. Data on the percent of infants discharged on a combination of enteral and parenteral support are not available. At discharge, approximately one quarter of the cohort were receiving exclusively formula feeds (24% for medical NEC, 27% for surgical NEC), half were

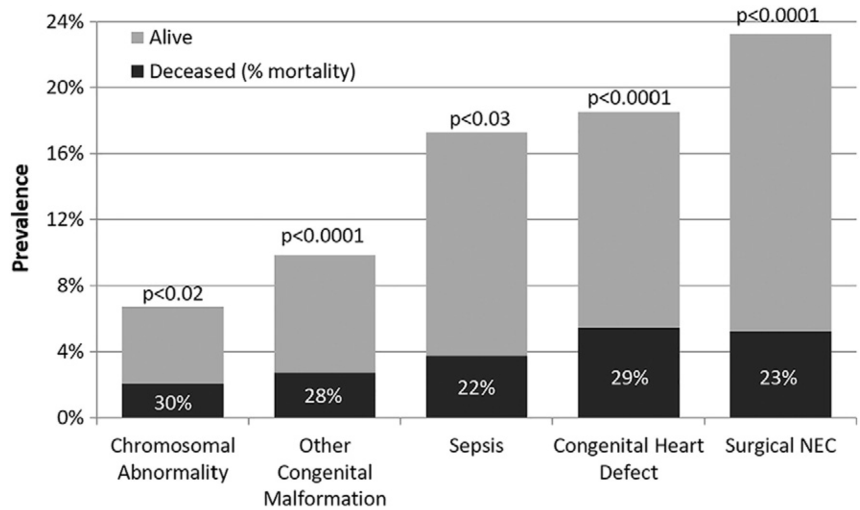

Fig. 1. Prevalence and percent mortality of significant independent predictors of death among >2500 g birth weight infants with necrotizing enterocolitis (n = 1629). Overall mortality in this cohort was 11%. NEC: necrotizing enterocolitis.

receiving a combination of human milk and fortifier or formula (50% for medical NEC, 53% for surgical NEC), and the rest were supported on exclusively human milk (19% for medical NEC and 18% for surgical NEC).

3. Discussion

Necrotizing enterocolitis, even among babies born >2500 g birth weight, carries significant morbidity and mortality. While efforts at preventing NEC are paramount and are well reported in the literature [9,10], this study focuses on the characteristics and outcomes of larger infants who have developed NEC. Among this heterogeneous cohort of infants who are diagnosed with NEC despite not being low birth weight, sepsis was the only preventable significant independent predictor of mortality and length of stay identified. Efforts to prevent sepsis, as well as timely diagnosis and treatment, should be a focus of quality improvement efforts to prevent the morbidity and mortality associated with NEC. Sepsis has previously been shown to be a significant risk factor for mortality in NEC [11,12]. Strategies for early detection of sepsis in very low birth weight infants such as predictive heart rate monitoring devices may be applicable to full term infants in the NICU [13].

NEC is a common and well recognized complication among very low birth weight neonates, while clinical suspicion is naturally lower for infants who do not have prematurity associated risk factors for NEC. A strength of this study is that strict criteria were required for the diagnosis of NEC, and only those with both clinical and radiographic evidence of NEC (minimum Bell's stage II) qualified for inclusion. Algorithms for NEC detection among very low birth weight infants have been developed, but it is unknown whether these are generalizable to other infants [14]. While compared to the general population, there was clearly a high prevalence of infants with congenital anomalies in this cohort [15], it is impossible to calculate from these data the risk factors for developing NEC among the full denominator of infants with birth weight > 2500 g, since the majority of normal birth weight babies do not require NICU admission.

Table 2
Independent risk factors for mortality.

	Affected (%)	Mortality (%)	ARR for mortality (95% CI)
Overall		11%	
Surgical NEC			
Yes	23%	22%	2.2 (1.7–2.9)[a]
No		8%	
Chromosomal abnormalities			
Yes	7%	30%	1.4 (0.9–2.0)
No		10%	
Congenital heart defects			3.5 (2.6–4.8)[a]
Yes	19%	29%	
No		7%	
Gastrointestinal defects			1.0 (0.7–1.4)
Yes	20%	11%	
No		12%	
Other congenital malformation			1.9 (1.4–2.7)[a]
Yes	10%	28%	
No		10%	
Sepsis			1.5 (1.1–2.0)[a]
Yes	17%	22%	
No		9%	

NEC: necrotizing enterocolitis. ARR: Adjusted Risk Ratio. In addition to the characteristics listed above, lower 1 min Apgar score was also an independent predictor of increased mortality (all $p < 0.05$).

[a] Indicates statistically significant differences between groups.

Table 3
Independent risk factors for increased length of stay among survivors.

	% of survivors affected	*Length of stay (days)*	*p-value*
		median (Q1, Q3)	
Overall		38 (24, 70)	
Surgical NEC			<0.0001
Yes	20%	62 (36, 94)	
No		34 (22,61)	
Chromosomal Abnormalities			<0.05
Yes	5%	69 (36, 127)	
No		37 (23, 68)	
Congenital heart defects			<0.0001
Yes	15%	70 (43, 117)	
No		34 (22, 63)	
Gastrointestinal defects			<0.0001
Yes	20%	60 (33, 98)	
No		35 (23, 62)	
Other congenital malformation			<0.0001
Yes	8%	77 (38, 133)	
No		36 (23, 68)	
Sepsis			<0.0001
Yes	15%	79 (44, 143)	
No		35 (22, 60)	

NEC: necrotizing enterocolitis. In addition to the characteristics listed above, lower 1 min Apgar score was also an independent predictor of longer length of stay among survivors (all $p < 0.05$).

Table 4
Growth from birth to hospital discharge among survivors with and without congenital anomalies.

	Medical NEC		Surgical NEC	
	N	*% or median (IQR)*	*N*	*% or median (IQR)*
Infants without any congenital anomalies				
Small for gestational age	692	6%	158	8%
<10th Percentile weight for age at discharge home	543	26%	144	35%
Birth weight (g)	693	3045 (2755, 3476)	158	3050 (2770, 3460)
Discharge weight (g)	691	3445 (3085, 3900)	157	3998 (3430, 4970)
Infants with congenital anomalies				
Small for gestational age	450	8%	136	12%
<10th Percentile weight for age at discharge home[a]	399	48%	117	44%
Birth weight (g)	451	3050 (2749, 3420)	136	2977 (2721, 3313)
Discharge weight (g)	449	4005 (3500, 4895)	134	4270 (3580, 5735)

NEC: Necrotizing Enterocolitis.
[a] Weight for age percentile not calculated for infants with <15 day length of stay.

Congenital heart disease (CHD) is frequently associated with NEC [4,16]; it has been shown to be associated with a 1.7-fold increase in NEC within the NICU population [17]. A prior Vermont Oxford Network study has shown that very low birth weight infants with CHD are at increased risk of NEC, and the current study supports that this increased risk also applies to term infants with CHD [4]. While the existence of congenital anomalies is not a modifiable risk factor, optimal management of these diseases to support intestinal perfusion and allow for safe enteral feeding may help mitigate the development and severity of NEC among these infants. Whether or not enteral feeds are causative for NEC in the CHD population is controversial [11,18]. In particular, the role of human milk compared with formula feeding seems to be associated with a reduction in the incidence of NEC [9]. Unfortunately, the current literature is represented by underpowered studies and more investigations are needed. Furthermore, an understanding of this increased risk of NEC can help guide healthcare providers in discussing the prognosis and expected outcomes of these complex patients.

Poor growth outcomes in this cohort are indicative of acute illness related malnutrition, a common problem among hospitalized pediatric patients [19,20]. In light of multiple studies demonstrating links between episodes of malnutrition in infancy and impairment in long-term neurocognitive outcomes, even in the context of full physical catch-up growth, aggressive optimization of nutrition in infants during their index hospitalization may have significant benefits [21]. Since many infants in this cohort require surgical correction for their congenital anomalies, addressing barriers to inadequate macronutrient delivery may support them through the metabolic stress of surgery and optimize surgical outcomes. This has been shown to improve outcomes in critically ill children [19,22]. Nutritional morbidity is high in this cohort, especially among those with preexisting congenital anomalies, and strategies for nutrition supplementation must be improved.

We report a low rate of PPD compared to initial laparotomy in this cohort. We found a 10% rate, with 77% of these patients going on to require laparotomy. Previous studies have shown a much higher rate of PPD ranging from 17% to 49% in surgically treated VLBW infants [23–25]. Moss et al. reported in a meta-analysis that higher birth weight infants were more likely to have laparotomy than PPD, which would explain the low rate of PPD in our cohort [26]. A more recent systematic review showed similar results regarding gestational age and birth weight [27], albeit a smaller difference than Moss [26]; in addition, there was a much higher rate of mortality in the PPD group. Those in our group with PPD alone also had a high rate of mortality. PPD was initially described for use in the extremely low birth weight (ELBW) population as in temporizing procedure for infants thought to be unlikely to survive a major laparotomy [28,29] and over the last 40 years has been used more commonly among this population. In this cohort, it is possible that more infants proceeded to laparotomy as the larger patients may be perceived as better able to tolerate an open laparotomy; may have been more stable and less physiologically deranged, and therefore able to tolerate proceeding to an operation; or may have, in fact, been sicker and therefore felt in more need of a more definitive operation. Indications for proceeding to laparotomy were not captured in these data, such that these arguments would all be speculative.

4. Limitations

For this study, the diagnosis of sepsis required positive cultures, but it is not possible to tell from these data whether bacteremia may be a result of NEC. Additionally, it is possible that malperfusion owing to sepsis may contribute to the development of NEC [30], making these intertwined variables impossible to analyze separately. The prevalence of congenital anomalies may be influenced by the population served at participating centers.

Regarding growth failure, this population had multiple other possible contributors to impaired growth regardless of NEC. Some children with congenital anomalies, especially those with chromosomal anomalies, may have differences in expected growth trajectory independent of nutritional factors [31–34]. Those with anomalies requiring neonatal surgical correction endured the inherent catabolic stress of surgery [35]. Some anomalies, including cyanotic congenital heart disease are intrinsically associated with increased caloric requirements to support growth [36].

5. Conclusion

Major congenital anomalies are present in nearly half of infants >2500 g birth weight who develop necrotizing enterocolitis. Morbidity and mortality increase with sepsis, surgical disease, and congenital anomalies. These infants have multiple potential risk factors for poor growth, and are at high risk for growth failure at discharge.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpedsurg.2017.10.028.

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Role of the authors

Velazco: Study conception and design, analysis and interpretation, drafting of the manuscript, critical revision, gave final approval.

Fullerton: Study conception and design, analysis and interpretation, drafting of the manuscript, critical revision, gave final approval.

Hong: Analysis and interpretation, participated in revision, critical revision, gave final approval.

Morrow: Study conception and design, data acquisition, analysis and interpretation, participated in drafting, critical revision, gave final approval.

Edwards: Study conception and design, data acquisition, analysis and interpretation, critical revision, gave final approval.

Soll: Study conception and design, data acquisition, analysis and interpretation, critical revision, gave final approval.

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Horbar: Study conception and design, data acquisition, analysis and interpretation, critical revision, gave final approval.

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