Characteristics and outcomes of a multi-institution cohort of infants with necrotizing enterocolitis totalis

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INTRODUCTION

Ten percent of neonatal intensive care deaths are attributed to necrotizing enterocolitis (NEC) [1]. Necrotizing enterocolitis totalis (tNEC), a rare form of NEC characterized by near-total bowel necrosis, is associated with almost 100% fatality [2]. Of infants who require surgery for NEC, 11% have tNEC [3], and, amongst those who die from NEC, 33% have total bowel necrosis[1]. However, the true incidence of this disease is not known, as tNEC cannot currently be preoperatively identified and is subjectively defined in the literature [2, 4].

Death from NEC has been associated with lower gestational age, lower birth weight, need for mechanical ventilation at diagnosis, and black race [5]. Although risk factors for NEC have been the subject of significant research [6], little is understood about which infants are susceptible to tNEC. Describing this unique cohort of infants is challenging, as single institutions may have few patients with the disease, and infants may die without surgery or require transfer for surgical care. Thus, the understanding of tNEC is limited to studies with small sample size [4, 7, 8]. As neonatal care advances and intestinal rehabilitation care improves, there is growing interest in the management and outcomes of infants with tNEC [2, 9–11]. The Children’s Hospitals Neonatal Database (CHND) provides prospectively collected data on rare conditions including NEC, allowing for better understanding of disease and the potential for outcomes prediction [12]. The primary purpose of this study was to describe the presentation at surgical referral of a large national cohort of tNEC infants and to compare presentation, surgical management, and mortality of tNEC infants to infants who require surgery for NEC but did not have totalis (sNEC).

METHODS

This was a multicenter retrospective cohort study with infants of all gestational ages receiving surgery for NEC identified in the CHND from January 2010 to December 2016. The CHND prospectively captures clinical data for infants admitted to 34 children’s hospitals whose neonatal intensive care units have at least a level IV designation, more than 400 annual admissions, and more than 50% of infants admitted are born outside the participating hospital [12]. Data collection methods and quality assurance measures have been published previously [3, 12]. Individual Institutional Review Boards (IRB) at participating centers approved participation in CHND, and the Emory University IRB exempted this study of retrospective analysis of de-identified data.

Infants admitted to a CHND center for the evaluation and treatment of NEC were identified. Those who had a diagnosis of NEC but never had surgery, had NEC surgery prior to admission to a CHND center, or whose NEC resolved prior to admission were excluded. To capture a similar clinical presentation and relative rapid surgical course for tNEC, we limited the cohort to infants who received surgery within five days of admission. As defined by the CHND, NEC requiring surgery was identified if an infant had clinical signs of NEC (bilious gastric aspirate or emesis, abdominal distention, or occult or gross blood in stool with no apparent rectal fissure) and radiographic findings (pneumatosis intestinalis, hepatobiliary gas, or pneumoperitoneum) and received one of the following surgeries: laparotomy, laparoscopy, ostomy creation for intestinal diversion, small bowel resection, large bowel resection, or primary intraperitoneal drain placement for treatment of NEC. Those with gastrointestinal anomalies including gastrochisis, omphalocele, bowel atresia, intestinal webs or stenosis, malrotation, and meconium ileus were excluded, as were infants with major or lethal congenital anomalies and those with cyanotic heart disease. Infants with focal intestinal perforation (FIP) identified at time of surgery, post-mortem, or with evidence of pneumoperitoneum without clinical signs of NEC were also excluded.

RESULTS:

Of 1059 infants, 161 (15.2%) had tNEC. Perinatal characteristics did not differ. tNEC infants were older and were less likely to have pneumoperitoneum at referral (5.6% vs 13.1%, p < 0.001) or intestinal perforation at surgery (38.5% vs 66.7%, p < 0.001). Infants with tNEC were more acidic preoperatively (7.1, [IQR 7, 7.3] vs 7.3, [IQR 7.2, 7.4], p < 0.001). Mortality was 96.9% for tNEC and 26.5% for sNEC (p < 0.001). tNEC cases varied by center, accounting for 0–43% of all surgical NEC cases.

CONCLUSIONS: Mortality is high for tNEC infants, who present at older age, with greater illness severity but are less likely to have intestinal perforation than sNEC infants.

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The study population was compared by the presence or absence of tNEC. tNEC, as defined in the CHND, was identified at the time of surgery or autopsy as such extensive large and small bowel involvement that the disease was considered lethal by the attending surgeon or pathologist respectively. The sNEC group included those infants who had NEC surgery, as defined above, but did not have totals. The study population was described using maternal, birth, and perinatal characteristics. Comorbidities at admission to CHND center were collected. Sepsis on admission was defined as a positive blood culture at the referring hospital or within 48 h of admission. Patent ductus arteriosus (PDA) was considered present prior to or at the time of referral if there was echocardiographic documentation from the referring center; pharmacologic treatment with indomethacin (prophylactic or treatment regimens), ibuprofen, or acetaminophen as well as surgical ligation were recorded. Perioperative characteristics, type of surgery, and post-surgical anatomy, when known, were collected. Short bowel syndrome/intestinal failure (SBS/IF) was identified when an infant had a major bowel resection (<75 cm or <50% of expected small bowel length remaining) and >90 days of parenteral nutrition. Mortality was assessed up to hospital discharge.

Statistical analysis

Data are presented as frequency and number for categorical variables and median and interquartile range (IQR) for continuous data. Comparisons of categorical variables used Chi-square test and Fisher’s exact as appropriate. Continuous variables were compared with the non-parametric Wilcoxon Rank Sum Test as departure from normality was observed. Statistical testing was two-sided. Individual center tNEC rate was calculated (percent of infants with NEC requiring surgery who had tNEC). The Wilson Score was used to calculate 95% confidence intervals for population proportions. Survival analysis using Kaplan–Meier curves was conducted to evaluate time to death, and Logrank test was used to compare groups. P value was considered significant at 0.05. All statistical analysis was performed in SAS Enterprise Guide 7.1 (Cary, NC).

RESULTS

Of 119,105 CHND admissions during the study period, 4708 had a diagnosis of NEC. Of those with a NEC diagnosis, 1406 infants had a NEC surgery within five days of admission (Fig. 1). Those with congenital anomalies, focal intestinal perforation or surgery prior to admission were excluded. The remaining 1059 infants comprised the study group, of whom 898 (84.8%) had sNEC and 161 (15.2%) had tNEC. Thirty-one of 34 CHND centers contributed patients to the study cohort. There were no statistically significant differences in demographic, perinatal and birth characteristics between groups (Table 1). There was a preponderance of male infants, 60%, which was not significantly different between the groups. The median gestational age and birth weight for the entire cohort were 27 weeks, (interquartile range (IQR) 25, 30 weeks) and 910 grams (IQR 700, 1382 grams), respectively; these were not different between tNEC and sNEC infants. The percentage of small for gestational age [13] infants was also not different between groups. Receipt of antenatal steroids was low in both groups (tNEC: 46.6%, sNEC 47.2%). tNEC infants had a trend towards higher cesarean section rate, but the difference did not reach statistical significance.

NEC diagnosis occurred five days later in tNEC infants (median 17 days [IQR 12, 17] vs 12 days [IQR 7, 25], p < 0.001) but at a similar postmenstrual age. At the time of surgical referral, tNEC infants were less likely to have severe IVH (tNEC 5.0% vs sNEC 10.5%, p = 0.029), to have received medical treatment for a PDA (tNEC 18.6% vs sNEC 26.1%, p = 0.048) or to present with intestinal perforation (tNEC 5.6% vs sNEC 13.1%, p = 0.005). There was no difference in the use of postnatal steroids. tNEC infants had greater need of intensive supportive care during transport and on arrival to referral centers including mechanical ventilation (tNEC 94.4% vs sNEC 80.2%), vasopressors (tNEC: 46.0% vs sNEC: 24.7%) and paralysis by neuromuscular blockade (tNEC 13% vs sNEC 2.7%) (all p < 0.001). Thirteen percent of all infants had a positive blood culture within 3 days of NEC surgery, and this rate did not differ between groups. Thirty percent of positive blood cultures were due to Escherichia coli and 23% to coagulase negative staphylococci.

The predominant surgery in both groups was a laparotomy. Only six (3.7%) infants with tNEC received a primary drain as the only surgical intervention (Table 2). Over half of sNEC infants were confirmed to have perforation at time of surgery, which was significantly more than their tNEC counterparts (tNEC 38.5% vs sNEC 66.7%, p < 0.001). SBS/IF was diagnosed in 180 (20.0%) of sNEC infants of whom 150 (83%) survived hospital discharge. Of the 71 sNEC infants with documentation of remaining bowel length, the median was 50 cm (IQR 34–70). Fifteen tNEC infants received an ostomy, 26 had small bowel resection and 12 had large bowel resection. Of the surviving tNEC patients, two had both large and small bowel resection, and two had just small bowel resection. However, none had documentation of length of bowel resected or length of bowel remaining. All were diagnosed with SBS/IF, and none were referred for bowel or liver transplant. No infant with tNEC received only a primary drain and survived. Time from NEC diagnosis to surgery was significantly associated with mortality with a median time to surgery of 1 day (IQR 0–2) for survivors and 0 days (IQR 0–1) for those who died, p < 0.001. This finding remained true when only looking at infants with sNEC (p = 0.016).

Overall mortality was 37% with a significant difference in time of death between groups (Fig. 2, logrank p < 0.001). Over half of the tNEC patients and a third of the sNEC patients died within 12 h of admission to a CHND center (Table 2). Intra-abdominal catastrophe was the primary cause of death in 94.2% of tNEC infants, while one third of sNEC cases had other attributable primary cause of death (i.e., multi-organ system failure in 14%, respiratory failure in 10%). Death or survival to discharge with SBS/IF occurred in 546 (51.6%) of all infants and in 388 (43.2%) of sNEC infants.

Twenty-seven out of 31 CHND centers contributed five or more patients to the entire study cohort; however, five centers had 10 or more tNEC cases contributing 36.8% to the total cohort and 53.4% to the sNEC group. To understand center variation, we compared the proportion of tNEC infants by center and cohort mortality by center (Fig. 3). The overall tNEC rate was 15% (95% CI 13–17%) which was unchanged after removing the four centers that contributed fewer than five patients to the total cohort. Across centers, the tNEC rate varied from 0–43%. One center had a statistically lower rate of tNEC (5%, 95% CI 2–12%) than for the
overall cohort and one had a higher rate (43%, 95% CI 33–54%). The overall mortality rate was 37.2% (95% CI 34–40%), which was also unchanged after removing the four centers with fewer than five patients. The range for overall NEC mortality was 11–63% with two centers below and two centers above the overall cohort mortality rate (Fig. 3).

DISCUSSION
This study is the largest multicenter cohort of infants with tNEC; in this group of infants who received surgery for NEC, we found 15% had tNEC and 97% of those infants died. Infants with tNEC were older at NEC diagnosis and less likely to present with bowel perforation than were infants without totalis. Given the significant burden of disease and catastrophic outcome, understanding differences in presentation and management for infants with tNEC may help clinicians caring for these infants and their families.

Our findings add to the limited literature on tNEC that was based primarily on retrospective studies by single institutions. Few consistent demographic variables, feeding data, or radiographic differences have been able to distinguish infants at-risk for tNEC [4, 7, 14]. A retrospective analysis from a single-center designed to develop a predictive totalis-score was limited by small numbers (13 tNEC cases) [8]. In our cohort, infants with tNEC, although older at presentation, had findings consistent with severe illness including more metabolic acidosis and an increased need for ventilator and blood pressure support. Time to death after NEC diagnosis for tNEC infants was significantly sooner than sNEC infants. Interestingly, those with tNEC had fewer common comorbidities of prematurity such as IVH and need for PDA treatment. Measures of illness severity, including preoperative inotrope use, mean blood pressure, and sepsis in addition to one-minute Apgar score were predictive of death or IF in a cohort of 147 surgical NEC patients [15]. The inclusion of one-minute Apgar score in this predictive model may be an attempt to account for unknown but important intrauterine factors. However, our larger cohort did not find differences in maternal conditions including chorioamnionitis, prolonged rupture of membranes, maternal hypertensive diseases, or placental abruption. We also found no difference in delivery room interventions including endotracheal intubation, epinephrine administration, or cardiac compressions. There was a trend towards a difference in cesarean section rates with a non-statistically significant higher rate in tNEC infants.

A unique finding in our study was the lack of perforation in the tNEC compared to sNEC infants, both at time of admission as recorded in admitting diagnoses as well as at time of surgery. Bowel perforation remains the clearest indication for surgery in infants with NEC, while declining physiologic state, portal venous gas, and abdominal wall erythema are relative indications [16]. The decision to proceed with surgery in tNEC may have been related

## Table 1. Demographic, birth and referral center admission characteristics for patients with sNEC and tNEC admitted to CHND centers between Jan 1, 2010 and Dec 31, 2016.

| Variable                        | All     | sNEC    | tNEC    | p     |
|---------------------------------|---------|---------|---------|-------|
| Total (%)                       | 1059    | 898 (85)| 161 (15)| –     |
| Gestational age (weeks)*        | 27 (25, 30) | 27 (25, 30) | 27 (25, 30) | 0.89  |
| Birth weight (grams)*           | 910 (700, 1382) | 920 (700, 1400) | 870 (715, 1220) | 0.62  |
| SGA ≤ 10% (%)                   | 178 (17) | 151 (17) | 27 (17)  | >0.99 |
| Female (%)                      | 423 (40)| 355 (40)| 68 (42)  | 0.54  |
| Maternal race (%)               |         |         |         | 0.08  |
| White                           | 449 (42)| 395 (44)| 54 (34)  |        |
| Black                           | 438 (41)| 359 (40)| 79 (49)  |        |
| Other                           | 122 (11)| 103 (12)| 19 (12)  |        |
| Hispanic (%)                    | 136 (13)| 119 (13)| 17 (11)  | 0.55  |
| Maternal conditions (%)         |         |         |         |       |
| Preterm labor                   | 445 (42)| 382 (43)| 63 (39)  | 0.44  |
| Prolonged ROM                   | 112 (11)| 97 (11) | 15 (9)   | 0.68  |
| Chorioamnionitis                | 100 (9) | 90 (10) | 10 (6)   | 0.14  |
| Maternal hypertension           | 222 (21)| 182 (20)| 40 (25)  | 0.21  |
| Placental abruptions            | 63 (6)  | 53 (6)  | 10 (6)   | 0.86  |
| Delivery room resuscitation (%) |         |         |         |       |
| Endotracheal ventilation        | 603 (57)| 514 (57)| 89 (55)  | 0.67  |
| Epinephrine administration      | 31 (3)  | 25 (3)  | 6 (4)    | 0.45  |
| Cardiac compressions            | 54 (5)  | 43 (5)  | 11 (7)   | 0.33  |
| Cesarean delivery (%)           | 651 (62)| 542 (60)| 109 (68) | 0.08  |
| Antenatal steroids (%)          | 494 (47)| 418 (47)| 76 (47)  | 0.93  |
| Postnatal steroids* (%)         | 436 (41)| 370 (41)| 66 (41)  | >0.99 |
| Surfactant, any (%)             | 673 (64)| 566 (63)| 107 (66) | 0.43  |
| Age at NEC Diagnosis (days)*    | 13 (7, 25)| 12 (7, 24)| 17 (12, 27) | <0.001 |
| PMA at NEC Diagnosis (weeks)*   | 30 (27, 33)| 30 (27, 33)| 30 (29, 32) | 0.55  |

sNEC Surgical necrotizing enterocolitis without totalis; tNEC Necrotizing enterocolitis totalis; CHND Children’s Hospitals Neonatal Database; IQR Interquartile range; SGA Small for gestational age, ROM Rupture of membranes, PMA Postmenstrual age.

*Median (25–75 percentile).

**Systemic steroids given prior to referral for any reason.
However, subjectivity likely does not explain all center variation. Varied widely with rates ranging from zero to 43%. Subjectivity, which may be re...methodology was similar to prior studies of surgical NEC patients. By limiting the cohort to a timeframe more consistent with FIP [18]. By limiting the cohort to surgical NEC patients was associated with decreased mortality in a literature review of 414 published cases [2]. As all pediatric cases of tNEC were included in the review, it is not clear that the improvement in mortality found with aggressive surgical management would translate to a neonatal population, especially one involving extremely premature infants who may have other significant comorbidities. An analogy to the infant with tNEC may be the decision regarding resuscitation of infant born at 22 weeks of gestational age. Hospital rates of initiating active treatment in infants born at 22 weeks account for variation between hospitals in survival and survival without neurodevelopmental impairment in these infants [20]. Perhaps there is a subgroup of tNEC patients who, with intervention, have potential for survival given the risk balance for long-term survival with SBS/IF after NEC [21, 22]. Clinicians have mixed opinions on management approaches to infants with tNEC. Data regarding survival without neurodevelopmental impairment in these infants [20]. Perhaps there is a subgroup of tNEC patients who, with intervention, have potential for survival given the risk balance for long-term survival with SBS/IF after NEC [21, 22]. Clinicians have mixed opinions on management approaches to infants with tNEC.

### Table 2. Perioperative, surgical characteristics and mortality of patients with sNEC and tNEC.

| Variable                                      | All     | sNEC    | tNEC    | P     |
|-----------------------------------------------|---------|---------|---------|-------|
| Total (%)                                     | 1059    | 898 (85) | 161 (15) | 0.001 |
| Age at NEC surgery (days)<sup>a</sup>         | 14 (7, 26) | 13 (7, 26) | 18 (12, 27) | 0.001 |
| PMA at NEC surgery (weeks)<sup>a</sup>        | 30 (28, 33) | 30 (27, 33) | 30 (29, 32) | 0.76  |
| Days from diagnosis to surgery<sup>a</sup>     | 0 (0, 1) | 0 (0, 1) | 0 (0, 2) | 0.001 |
| Perioperative bacteremia<sup>a</sup> (%)      | 140 (13) | 119 (13) | 21 (13) | >0.99 |
| Preoperative pH<sup>bc</sup>                  | 7.3 (7.2, 7.3) | 7.3 (7.2, 7.4) | 7.1 (7.0, 7.3) | <0.001 |
| Preoperative pCO<sub>2</sub><sup>ac</sup> (%)  | 48 (39, 58) | 48 (39, 57) | 47 (37, 61) | 0.88  |
| Preoperative glucose<sup>ac</sup> (%)         | 102 (79, 146) | 101 (79, 140) | 109 (76, 186) | 0.12  |
| NEC surgery type                              |         |         |         | <0.001 |
| Laparotomy (%)                                | 759 (72) | 627 (70) | 132 (82) |       |
| Primary drain (%)                             | 159 (15) | 146 (16) | 6 (4) |       |
| Laparotomy and drain (%)                     | 139 (13) | 116 (13) | 23 (14) |       |
| Perforation at surgery (%)                    | 661 (62) | 599 (66.7) | 62 (39) | <0.001 |
| Bowl remaining, cm (n = 71)<sup>a</sup>       | 50 (34, 70) | 50 (34, 7) |         |       |
| Second look surgery (%)                       | 141 (13) | 137 (15) | 4 (3) | <0.001 |
| SBS/IF among survivors (%)                   | 154 (15) | 150 (17) | 4 (3) | <0.001 |
| Transfer for transplant (%)                  | 2 (0.2) | 2 (0.2) | 0 (--) | >0.99 |
| Mortality (%)                                 | 392 (37) | 238 (27) | 156 (97) | <0.001 |
| Death ≤ 12 h from admission (%)              | 163 (41) | 81 (34) | 82 (53) | <0.001 |

sNEC Surgical necrotizing enterocolitis without totalis, tNEC Necrotizing enterocolitis totalis, IQR interquartile range, PMA Postmenstrual age, SBS Short bowel syndrome/intestinal failure.

<sup>a</sup>Median (25th-75th percentiles)
<sup>b</sup>Positive culture within three days of surgical procedure
<sup>c</sup>Number missing data for preoperative labs included: sNEC: pH, pCO<sub>2</sub>, glucose. tNEC: pH, pCO<sub>2</sub>, glucose

A recent systematic review on pediatric tNEC found that over 50% of published reports had no clear definition of tNEC, and those that did define the disease had variable definitions [2]. This review, it is not clear that the improvement in mortality found with aggressive surgical management would translate to a neonatal population, especially one involving extremely premature infants who may have other significant comorbidities. An analogy to the infant with tNEC may be the decision regarding resuscitation of infant born at 22 weeks of gestational age. Hospital rates of initiating active treatment in infants born at 22 weeks account for variation between hospitals in survival and survival without neurodevelopmental impairment in these infants [20]. Perhaps there is a subgroup of tNEC patients who, with intervention, have potential for survival given the risk balance for long-term survival with SBS/IF after NEC [21, 22]. 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between FIP and sNEC may have resulted in some FIP cases in the sNEC group. It is less likely the tNEC group had contamination given the low rate of peritoneal drain as the sole operative management approach. And finally, the database is limited in granular data such as specific laboratory values perhaps contributing to the lack of definitive clinical markers to help identify at-risk patients, leading to an opportunity for further potential for collaboration across centers.

tNEC is a rare disease in neonates; however, in those infants referred for surgical evaluation due to NEC, it can be present in 15% of cases. In our population, infants with tNEC were older at presentation and were less likely to have an intestinal perforation. The rates of tNEC varied by center, and this variation may be related to differences in practice and the subjective nature of tNEC definition. Collaborative efforts are needed to uniformly document surgical procedures and agreed upon definitions in order to impact practices and outcomes. Currently tNEC consistently results in almost definitive mortality; but, as clinicians deliberate alternative interventions other than palliation, with improved gastrointestinal rehabilitation and engagement of parents, the potential for post-discharge survival may be possible in certain infants.

Fig. 2 Kaplan-Meier Survival curves by necrotizing enterocolitis typic. Time to death is significantly different between tNEC and sNEC infants. (Logrank p < 0.001).

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AUTHOR CONTRIBUTIONS

ATR and AJP conceptualized and designed the study, interpreted the results, drafted the initial manuscript, reviewed and revised the manuscript, and participated in funding acquisition. IZ participated in study design, data analysis, and reviewed and revised the manuscript. MTS conceptualized and designed the study, reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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COMPETING INTERESTS

All listed authors declare no real or perceived conflicts of interest with the exception of Isabella Zaniletti, who is an employee of the Children’s Hospital Association, Inc (Overland Park, KS) which designed, launched and maintained the database used in this study from 2012–2016.

ADDITIONAL INFORMATION

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