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Necrotizing enterocolitis totalis: High mortality in the absence of an aggressive surgical approach

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ABSTRACT

Background: Necrotizing enterocolitis is the leading case of gastrointestinal-related morbidity in premature infants. Necrotizing enterocolitis totalis is an aggressive form of necrotizing enterocolitis, which has traditionally been managed with comfort care. Recent advances in management of short bowel syndrome have resulted in some reported long-term survival.

Methods: Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, studies that reported outcomes in children with necrotizing enterocolitis totalis were identified. The definition of necrotizing enterocolitis totalis was captured along with length of follow-up, patient demographics, and outcomes.

Results: A total of 766 articles were screened, of which 166 were selected for full article review. Of these, 32 articles included data on 414 patients with necrotizing enterocolitis totalis. In the majority of studies (52%), necrotizing enterocolitis totalis was not defined. Aggressive surgical therapy (defined as bowel resection or fecal diversion) was undertaken in 32 patients (7.7%), with a mortality rate of 68.8%. In contrast, nonaggressive surgical therapy was undertaken in 382 patients (92.3%), and the mortality in these patients was 95%. Long-term outcomes for necrotizing enterocolitis totalis survivors, such as length of time on parenteral nutrition, progression to liver and/or small bowel transplant, and quality of life, were not reported.

Conclusion: We found that there is no accepted definition of necrotizing enterocolitis totalis. Aggressive surgical therapy is rarely pursued, which likely drives the overall high mortality rate. This study underscores the importance of standardizing the definition of necrotizing enterocolitis totalis and capturing short and long-term outcomes prospectively. With more aggressive surgical therapy, more infants are likely to survive this abdominal catastrophe, which was once thought to be uniformly fatal.

Introduction

Necrotizing enterocolitis (NEC) is the leading gastrointestinal cause of morbidity and mortality in neonates.[1,2] The range of clinical presentations of NEC is broad. Some patients may improve with a course of antibiotics and bowel rest, and others require surgery. Mortality rates in this patient population are high, especially in neonates who undergo surgery. NEC managed medically is associated with a 21% mortality rate, compared with a mortality rate of 35% in patients with surgical NEC.[3,4] These mortality rates are even higher in patients with low birth weights (ie, 500–700 grams) and in patients with congenital heart disease.[5–8] The most challenging group to manage is the subset of patients with NEC who have necrosis of the entire small intestine. Commonly referred to as necrotizing enterocolitis totalis (NEC-T), this represents a particularly aggressive form of NEC, associated with a high mortality rate. Studies report the incidence of NEC-T to be as high as 10% of all neonates diagnosed with NEC.[9,10]

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No specific definition of NEC-T has emerged among clinicians or in the medical literature. Some may consider an infant to have NEC-T when the entire small bowel is involved, or if there is patchy involvement of extensive segments of bowel. Others use the term to describe patients with involvement of the small and large bowel. This heterogeneity is reflected in the literature, where terms used to describe this entity include fulminant NEC, pan-intestinal NEC, and generalized NEC, among others. Historically, patients found to have NEC-T on laparotomy have not been offered bowel resections or ongoing resuscitation because of the belief that long-term survival is very poor.

Counseling parents regarding decision-making in these difficult cases is challenging given the lack of a uniform definition for NEC-T. There is also a paucity of outcomes data for these patients, because aggressive treatment is not routinely offered to patients clinically diagnosed with NEC-T. In the past decade, advancements have been made in the management of patients with short bowel syndrome (SBS), and contemporary data demonstrate improved survival in patients requiring long-term parenteral nutrition (TPN).[11,12] These factors further confound discussions among parents and providers when considering treatment options in patients with NEC-T.

To address these knowledge gaps, we conducted a systematic review of the literature in to (1) better understand how NEC-T is defined, (2) understand the proportion of reported cases in whom aggressive treatment was pursued once the diagnosis of NEC-T was made, and (3) quantify mortality in patients with NEC-T.

Methods

Reporting and registration

This systematic review was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[13] This study was declared exempt from review by the Nemours Institutional Review Board (Wilmington, DE).

Search strategy

Independent review of the PubMed, MEDLINE, Scopus, CINAHL, and Google Scholar databases was undertaken to search publications in the English language regarding patients 18 years of age or younger. Key words used to identify studies that included patients with NEC included: enterocolitis, necrotizing, NEC, totalis, fulminant, intestinal totalis, pan totalis, surgery, and pediatric. Individual search strings that were used are listed in the Appendix. The literature search was performed by one individual (K.F.), who also removed duplicate articles. After the identification of the articles by titles, the abstracts were reviewed by three individuals (K.D., K.F., L.B.) independently. Consensus between all three reviewers was required for an article to be considered for full article review. Articles that were identified for full article review were distributed among ten reviewers (K.D., A.M., C.D., J.M., K.S., C.L., S.P., K.F., C.V., L.B.). The full text of each article was reviewed, and data on patients with NEC-T were extracted.

Covariates and outcomes

Data that were extracted included the definition for NEC-T, patient demographics, treatment strategies, length of follow-up, and patient outcomes. The definition of NEC-T was captured as specified verbatim in each article. Each definition was then recategorized along an anatomic spectrum that included the following: involvement of small bowel only; involvement of small bowel and other viscera, such as the colon or stomach (ie, pan intestinal); or involvement of a defined (ie, quantified segment) segment of bowel. If a definition was not provided, it was designated in an undefined category. The treatment modality that was offered to these patients was also captured and defined as aggressive therapy if an attempt was made to perform bowel resection and/or fecal diversion, or nonaggressive therapy (ie, exploratory laparotomy only). Outcome measures, including length of follow-up, long-term morbidity, and mortality, were captured.

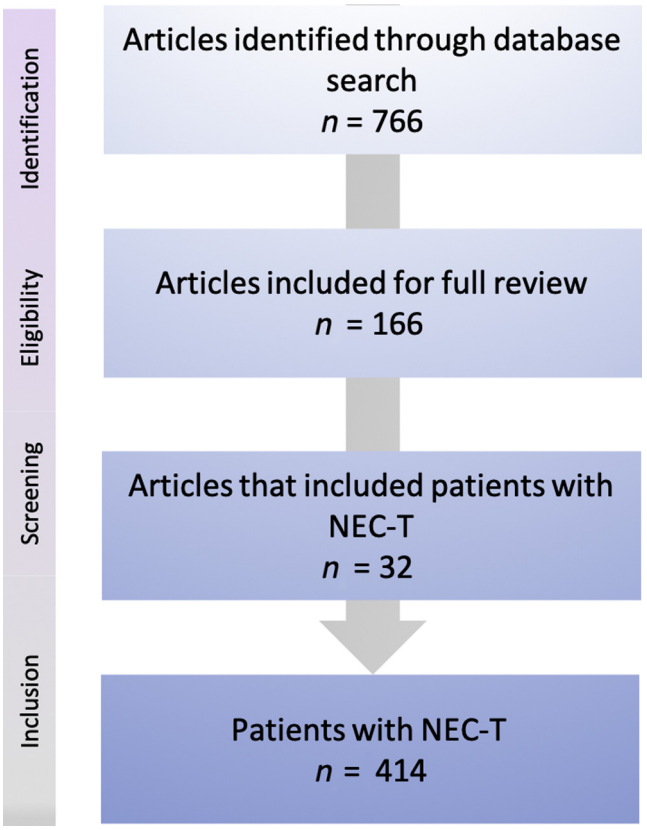

Fig 1. PRISMA flowchart for study selection. *PRISMA*, Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Results

The initial search resulted in 766 abstracts published between the years 1973 and 2016. Of these, 166 articles were included for full article review. Of the 166 articles, only 32 articles included data on patients with NEC-T (Fig 1 and the Table).

The definitions for NEC-T used in the literature were variable (Fig 2). In the included articles, NEC-T was most frequently undefined (52%). The term "pan intestinal," which was used to describe NEC-T where both large and small bowel were involved, was used in 30% of the articles. In 9% of articles, the term "NEC-T" was used to describe patients with involvement of the small bowel only. The segment of bowel involved was quantified in the remaining 9% of articles; however, this was also variable and ranged anywhere from 75%–100% of small bowel and/or large bowel.

A total of 414 patients with NEC-T were identified. NEC-T was most commonly diagnosed at the time of laparotomy, but diagnosis at autopsy was discussed in 2 articles.[14,15] Data regarding morbidity and long-term outcomes were rarely reported. Follow-up was also variable and ranged from 3 days to 5 years (Table). Mortality rates were reported in 347 patients, of which 326 succumbed to NEC-T, resulting in an aggregate mortality rate of 93.9% in all patients with NEC-T identified in the literature.

Table
Studies included in this systematic review

Author	Year	Definition	Was aggressive therapy offered?	Number of patients	Mortality	Follow-up period
Dudgeon et al[15]	1973	Small bowel only	No	1	1	n/a
Livaditis et al[29]	1974	Small bowel only	No	1	1	13 days
Mollitt et al[30]	1982	Small bowel only	No	3	3	n/a
Aszodi[31]	1984	Quantified Segment	Yes	9	9	n/a
Cikrit et al[32]	1984	Pan intestinal	No	34	34	n/a
Ricketts[33]	1984	Undefined	No	9	7	n/a
Cikrit et al[34]	1985	Undefined	No	29	26	n/a
Zamir et al[35]	1988	Undefined	No	20	14	n/a
Fleischman et al[36]	1990	Pan intestinal	No	1	1	12 days
Parigi et al[37]	1994	Undefined	No	4	4	3 days
Fasching et al[38]	1994	Pan intestinal	No	2	2	0 days
Limmer et al[39]	1994	Pan intestinal	No	8	8	n/a
Gambarara et al[40]	1999	Pan intestinal	Yes	1	0	3 months
Fasoli et al[41]	1999	Pan intestinal	Yes	12	8	25-111 days
Rovin et al[42]	1999	Undefined	No	1	1	n/a
Lessin et al[43]	2000	Undefined	Yes	2	1	1-4 years
Molik et al[44]	2001	Undefined	No	10	10	n/a
Banieghbal et al[45]	2004	Pan intestinal	No	77	77	3 months
Tannuri et al[46]	2004	Pan intestinal	Yes	1	0	19 months
Roy et al[47]	2005	Undefined	No	5	4	n/a
de Souza et al[48]	2009	Quantified segment	No	16	n/a	n/a
Takeda et al[49]	2010	Undefined	Yes	1	0	5 years
Numanoglu et al[50]	2011	Undefined	No	1	1	n/a
Thyoka et al[51]	2011	Undefined	Yes	6	4	n/a
Thompson et al[14]	2011	Quantified segment	No	39	n/a	n/a
Benkoe et al[52]	2012	Pan intestinal	No	7	n/a	n/a
Pang et al[53]	2012	Undefined	No	2	2	n/a
Bhatia et al[54]	2014	Undefined	No	4	4	n/a
Sho et al[55]	2014	Undefined	No	13	13	n/a
Murthy K et al[10]	2014	Undefined	No	84	80	n/a
Wright et al[56]	2014	Undefined	No	5	5	n/a
Sheng et al[57]	2016	Undefined	No	6	6	n/a

Aggressive surgical therapy was undertaken in only 32 patients (7.7%), reported in 7 articles. Length of bowel resected and long-term outcomes were not consistently reported in these patients, and follow-up ranged from 3 months to 5 years. Mortality in patients who had aggressive surgical therapy was 68.8% (22/32 patients). In contrast, 382 patients (92.3%) had nonaggressive surgical therapy, reported in 25 articles. Mortality rates were reported in 320 patients, and 304 patients died because of NEC-T, resulting in a mortality of 95% in this cohort (Fig 3). Lastly, pursing nonaggressive surgical therapy in NEC-T is a trend that appears to have remained stable over time (Fig 4).

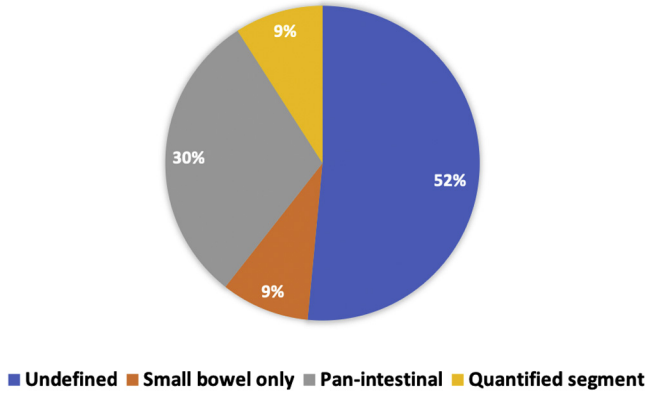

Fig 2. Definitions of NEC-T. *NECT-T,* necrotizing enterocolitis totalis.

Discussion

NEC-T is a severe form of necrotizing enterocolitis that causes significant mortality and morbidity in neonates.[10] A thorough and complete understanding of outcomes associated with NEC-T has been hampered by a lack of uniform diagnostic criteria and a failure to provide aggressive surgical therapy in the vast majority of cases.

For providers to reliably offer evidence-based prognosis counseling and to help facilitate decision-making, it is essential to clearly define NEC-T. In this literature review, the majority of articles provided no definition of NEC-T, and definitions were highly variable among the articles that did define it. We also found that the majority of patients underwent exploratory laparotomy only, with no bowel resection or fecal diversion. This trend of offering nonaggressive surgical therapy does not appear to have changed from the early 1970s to 2016. Although the overall mortality rate in patients with NEC-T is high, this is driven largely by the greater than 90% of patients reported in the literature who did not receive aggressive surgical therapy. If life-prolonging therapy is to be pursued after the diagnosis of NEC-T has been made, removing the septic source (ie, the nonviable intestine) is essential. In the 7.7% of patients who had aggressive surgical therapy, the mortality rate was 68.8% compared with 95% in those who exclusively had nonaggressive surgical therapy (ie, exploratory laparotomy only). This suggests a more aggressive approach to treating patients with NEC-T may have an impact on mortality. This, coupled with significant advances in care for children with short bowel syndrome, supports the notion that NEC-T should no longer be considered a uniformly lethal condition.

When resection is undertaken in neonates with NEC-T, all of these patients will have SBS. Gestational age is a critical consideration at the time of surgery, because the length of small bowel more than doubles from 70 cm in neonates at 24–26 weeks gestation to more than 150 cm in full-term neonates.[16] The involved segment of bowel, presence or absence of the ileocecal valve, presence of at least some colon, and the length of residual small intestine are data

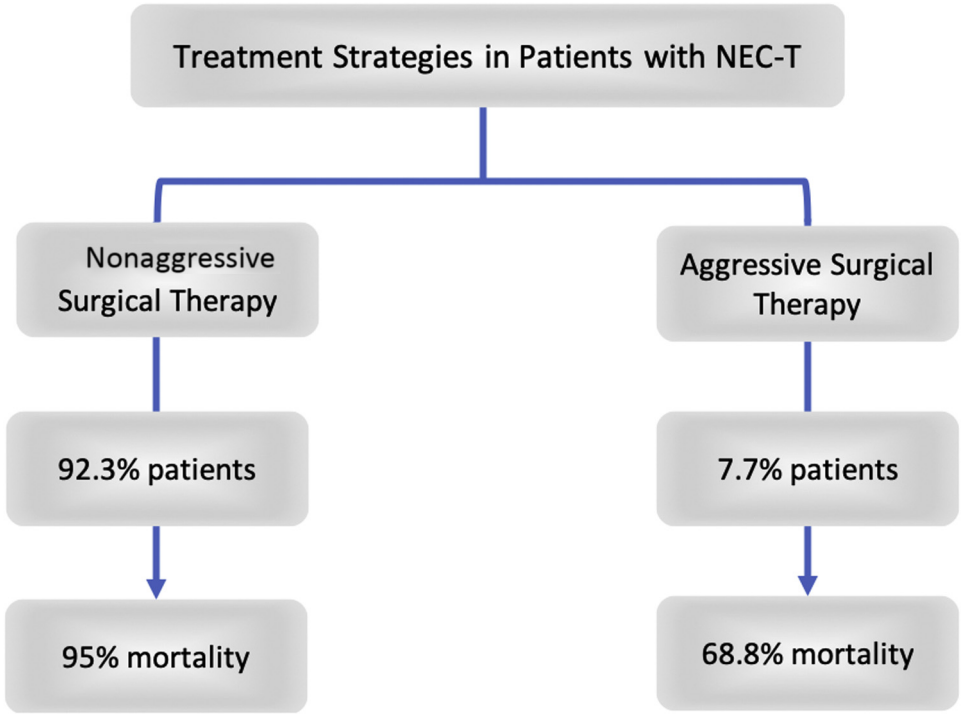

Fig 3. Treatment strategies and mortality rates in patients with NEC-T: Nonaggressive surgical therapy (exploratory laparotomy only) versus aggressive surgical therapy (ie, bowel resection or fecal diversion). *NECT-T,* necrotizing enterocolitis totalis.

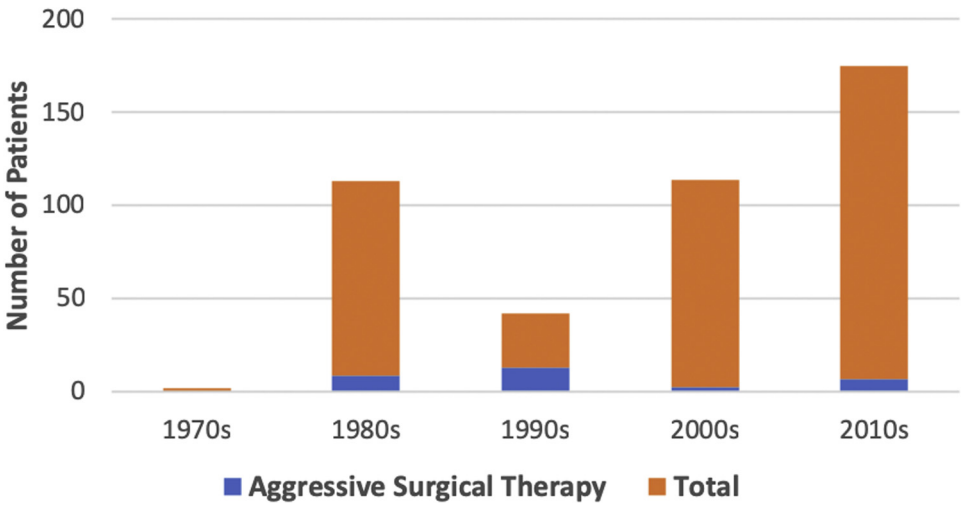

Fig 4. Number of patients with NEC-T who received aggressive surgical therapy (ie, bowel resection or fecal diversion) compared with the total number of patients with NEC-T in each decade. *NECT-T,* necrotizing enterocolitis totalis.

that are critical determinants of long-term outcomes and achievement of enteral autonomy in patients with SBS.[17,18]

For patients who never reach enteral autonomy, outcomes on long-term TPN are increasingly promising.[19,20] It is important to note the shift to an emphasis on intestinal rehabilitation from intestinal transplantation.[21,22] This has occurred in part because of strategies that have decreased complications associated with intravenous access and new lipid formulations that have led to a decrease in intestinal failure associated liver disease.[23–25] In contemporary reports of patients with SBS after NEC, survival rates range anywhere from 80%–100%.[19–21,26] It should be noted, however, that these reports also suffer from a lack of consistent terminology regarding residual length of intestine, and many included patients with less significant bowel resections than might be expected in cases of NEC-T.

Despite data showing favorable outcomes in patients with intestinal failure, the findings in this systematic review suggest that the majority of providers still do not appear to offer aggressive surgical therapy. Surveys of neonatologists and pediatric surgeons have also shown that both groups are more likely to recommend comfort care in patients with NEC who will require extensive bowel resections.[27,28] These surveys not only underscore the ongoing need for education of providers on long-term outcomes in patients with NEC-T and SBS, but also the need for a paradigm shift in how families are counseled. Considering the fact that long-term survival can exceed 80% for infants with SBS secondary to NEC, the historical

approach of offering comfort care only for patients with NEC-T should be abandoned.[12,19–21] Providers should present both comfort care and aggressive measures when counseling families. The final recommendation should be based on prognosis and parental wishes concerning quality of life with a chronic, technology-dependent medical condition.

This study has several limitations that are important to consider. In this literature review, the data summarized represent a heterogenous patient population. Important details, such as the gestational age at the time of surgery, length of bowel resected in patients who had aggressive surgical therapy, patient comorbidities, and long-term outcomes data were rarely available. Although there appeared to be a survival advantage for patients who had aggressive surgical therapy compared with nonaggressive surgical therapy, we were unable to determine why aggressive therapy was pursued rather than comfort care in these cases.

This study underscores the importance of standardizing the definition of the term "NEC-T" to effectively capture patient outcomes prospectively. This goal could be achieved via utilization of a Delphi-based process to establish a definition for NEC-T based on anatomic descriptors. Establishment of a national database to capture data—including gestational age, weight, and height at diagnosis; comorbidities; length of residual bowel; involved segments of the gastrointestinal tract (duodenum, jeujunoileum, colon); and presence or absence of the ileocecal valve—will be essential. Ideally, such a database would track long-term outcomes, including length of TPN dependence, need for transplantation, and quality-of-life measures. This will facilitate the establishment of a standardized definition and capture essential variables to inform future investigations. It will also help us to better understand not only which infants are more likely to survive with aggressive surgical therapy, but also quantify the need for long-term TPN and its associated complications.

The management of patients with NEC-T and the resultant SBS is certainly complex and requires an experienced multidisciplinary team. The availability of high-quality comparative data would bring clarity to complex discussions regarding the pursuit of aggressive surgical therapy versus comfort care and would help providers guide parents to make informed decisions that are consistent with their values.

Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Appendix

Search strategy and string

Limit – English, all child (0-18 years)

PubMed

(((((“Intestines”[Mesh]) OR intestines) OR intestine)) AND (((“General Surgery”[Mesh] OR “Surgical Procedures, Operative” [Mesh]) OR “surgery”[Subheading]) OR (“therapy”[Subheading] OR “Therapeutics”[Mesh]))) AND (((((((((“necrotizing enterocolitis” AND totalis) OR nec totalis) OR intestinal totalis) OR pan intestinal) OR pan totalis) OR totalis) OR “Enterocolitis, Necrotizing”[Mesh]) OR “Enterocolitis, Necrotizing”[Mesh] AND totalis) OR necrotizing enterocolitis)

Scopus

(TITLE-ABS-KEY (surgery AND (“necrotizing enterocolitis” OR “nec totalis” OR “fulminant” OR “intestinal totalis” OR “pan totalis”)) AND (intestine) AND (pediatric) AND (LIMIT-TO (DOCTYPE , “ar”) OR LIMIT-TO (DOCTYPE , “re”) OR LIMIT-TO (DOCTYPE , “cp”)) AND (EXCLUDE (PUBYEAR , 2018)) AND (LIMIT-TO (LANGUAGE , “English”))

CINAHL

(((MH “Enterocolitis, Necrotizing”) OR “necrotizing enterocolitis” OR NEC OR “NEC totalis” OR “fulminant enterocolitis” OR “intestinal totalis” OR pan totalis”)) AND ((MH “Therapeutics”) OR therapy OR “general surgery”)) AND ((MH “intestines”) OR intestine)

MEDLINE

((“necrotizing enterocolitis” OR Enterocolitis, Necrotizing/ OR nec OR “nec totalis” OR fulminant OR “intestinal totalis” OR “pan totalis”) AND ((surgery OR “General Surgery/”) OR (Therapeutics/ OR therapy)))

GoogleScholar

((((((“necrotizing enterocolitis”) OR NEC) OR “NEC totalis”) OR “fulminant enterocolitis”) OR “intestinal totalis”) OR “pan totalis”)))))) AND “general surgery”))))))) AND pediatric* AND “peer review”

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