



Comparison of Clinical Presentation and Outcome of Necrotizing Enterocolitis and Non-NEC Focal Intestinal Perforation in Extremely Low Birth Weight Neonates – Theory of Natural Selection: A Surgical Perspective

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Abstract

Overview

- Necrotizing Enterocolitis (NEC) with perforation and focal intestinal perforation (FIP) are major causes of morbidity affecting extremely low birth weight infants (ELBW).
- The pathogenesis of the two groups continue to remain controversial and outcome unpredictable.
- Often clubbed together, FIP is now distinguished as a definite clinical entity with different pathogenesis and outcome variables.

Study Objective: To review and study clinical characteristics and clinico-pathologic cause of bowel perforation in NEC and Non-NEC FIP neonates with ELBW at a suburban children's hospital (Children's Hospital Malad West Mumbai) in a developing Low-Middle Income Country (LMIC). To further evaluate the surgical procedures, and the survival and outcome of ELBW neonates with NEC and FIP. Authors propose a theory namely "Theory of Natural Selection" for FIP as opposed to universal inflammatory changes in the NEC group to elucidate the difference between the two groups and help to predict outcome.

Methods: ELBW neonates (< 1000 gms) admitted with NEC perforations and non-NEC FIP were analyzed retrospectively over a four-year period. The data sheets analyzed regarding age of presentation, clinico-pathologic cause of bowel perforation, management offered, and subsequent outcome achieved. NEC neonates without evidence of perforation and those where perforations were secondary to mechanical causes were excluded from the study. There was a total of fifty-four neonates diagnosed with pneumoperitoneum. NEC (33 babies) remained the single major cause of pneumoperitoneum in the newborn (61%). However, in 21 (39%) neonates, the cause was not related to NEC – gastric perforations (6), isolated colorectal perforations (5), cecal perforations (3) and duodenal perforations (2). In other five cases no cause could be found. Co-morbid factors were present in 90%, with prematurity as the leading factor in 28 babies (52%). Twenty-One of those 28 were ELBW neonates (< 1000 gms). Only sixteen of those twenty-one babies were selected for the study.

Results

NEC Group (33): 9 out of 33 NEC babies (27%) were ELBW with perforations.

Non-NEC Group (21): Twelve of the twenty-one babies with non-NEC perforations (57%) qualified as FIPs; the other nine neonates had mechanical cause for perforations and had to be excluded from the study. Out of total of 21 babies in the Non-NEC Group, only seven qualified for the study. The other five ELBW had mechanical cause for perforations: Gastric perforations: 3, Cecal perforation: 1 and two neonates had duodenal perforations secondary to neonatal intestinal obstruction.

Clinical Characteristics of Perforations and Clinico-Pathologic Correlations

NEC Group: All the nine babies in the group had universal inflammatory changes throughout the small and large intestines. These babies had a very fast progression of symptoms, tended to be sicker in a shorter span and were unstable pre-operatively. Intra-operative quick lavage with drainage with stomas was mainstay of surgical treatment. More than half of them required two or more operative procedures. Post-operatively these babies had a longer hospital stay. Mortality was higher compared to non-NEC FIP group.

Non-NEC FIP Group: The inflammatory changes were less florid; mostly localized to one segment of bowel usually terminal ileum or cecum / colon or rectum in one instance. There was a large perforation with dehiscence of almost up to one third segment of anti-mesenteric bowel wall. Despite such large perforation, the infection was rather localized. Interestingly this group was relatively less unstable pre-operatively, did well intra-operatively with resection anastomosis, usually ended without stomas and had a shorter hospital stay. Mortality was lower in this group compared to the NEC group. The authors hence propose a "Theory of Natural Selection" in Non-NEC FIP neonates where in nature localizes the inflammatory process to one segment of bowel over a period such that peritoneal processes can wall off the perforation preventing generalized sepsis. Timely surgical intervention should predict a reasonably good outcome.

Conclusion: It should be possible to differentiate between NEC perforations and non-NEC FIP depending on clinical characteristics and parameters available. Prospective randomized trials along with histo-pathologic correlation should be done to prove "Theory of Natural Selection" and identify factors for localization of inflammatory changes in non-NEC FIP neonates as compared to NEC neonates thus enabling to predict a favorable outcome for this cohort of neonates.

Keywords: Necrotizing enterocolitis; focal intestinal perforation; ELBW (extremely low birth weight infants)

Introduction

Necrotizing enterocolitis (NEC) and focal (syn. idiopathic or spontaneous) intestinal perforation (FIP) are the most important acquired intestinal diseases in preterm infants with very low birth weight <1500 g (VLBW) [1]. In preterm NEC, feeding difficulties, bacterial overgrowth, ileus, and compromise of innate intestinal defenses may cause inflammation in intestinal villi and ischemia [2]. Most infants with FIP are extremely premature, develop gastrointestinal symptoms during their first week of life, and show rapid progress towards serious life-threatening illness [3-5]. Infants with NEC may be older and more mature at birth, but NEC and FIP may be clinically indistinguishable and definitive diagnosis often requires intervention of a pediatric surgeon (PS) [6,7].

Questions to Answer

- Is it possible for neonatologists to possibly differentiate between NEC perforations and non-NEC FIP depending on clinical characteristics and parameters available.
- Do differences in the frequency of NEC and FIP between birth weight strata of VLBW infants indicate a greater need for surgical intervention by PS?

c) The authors hence propose a "Theory of Natural Selection" in Non-NEC FIP neonates where in nature localizes the inflammatory process to one segment of bowel over a period of time such that peritoneal processes are able to wall off the perforation preventing generalized sepsis.

d) Lastly Timely surgical intervention by PS should predict a reasonably good outcome.

Materials and Methods

ELBW neonates (< 1000 gms) admitted with NEC perforations and non-NEC FIP were analyzed retrospectively over a four-year period. The data sheets analyzed regarding age of presentation, clinico-pathologic cause of bowel perforation, management offered, and subsequent outcome achieved. NEC neonates without evidence of perforation and those where perforations were secondary to mechanical causes were excluded from the study. There was a total of fifty-four neonates diagnosed with pneumoperitoneum. NEC (33 babies) remained the single major cause of pneumoperitoneum in the newborn (61%). However, in 21 (39%) neonates, the cause was not related to NEC - gastric perforations (6), isolated colorectal

perforations (5), cecal perforations (3) and duodenal perforations (2). In other five cases no cause could be found. Co-morbid factors were present in 90%, with prematurity as the leading factor in 28 babies (52%). Twenty-One of those 28 were ELBW neonates (< 1000 gms). Only sixteen of those twenty-one babies were selected for the study.

Table 1

Total Babies with Pneumoperitoneum (54)	ELBW (16)	Mortality (6)
NEC Group: 33	9	5 (56%)
Non-NEC Group (Focal Intestinal Perforations): 21	7	1 (14%)
Non-NEC Group (Focal Intestinal Perforations): 21	ELBW: 12 (7/12 Qualified for Study)	
Focal Intestinal Perforations (Qualified for study)12	7	
Mechanical Causes for Perforations (Not Qualifying for study - Excluded) 9	5	1 (14%)

Non-NEC Group (21)

Twelve of the twenty-one babies with non-NEC perforations (57%) qualified as FIPs; the other nine neonates had mechanical cause for perforations and had to be excluded from the study. Out

Results

NEC Group (33)

9 out of 33 NEC babies (27%) were ELBW with perforations (Table 1).

of total of 21 babies in the Non-NEC Group, only seven qualified for the study (Table 2). Other five ELBW had mechanical cause for perforations: Gastric perforations: 3, Cecal perforation: 1 and two neonates had duodenal perforations secondary to neonatal intestinal obstruction (Table 3).

Table 2

Non-NEC Group (Focal Intestinal Perforations) (12)	ELBW (7)
No Cause Found 5	3
Isolated Colo-Rectal Perforations 5	3
Cecal Perforations 2	1

Table 3

Mechanical Causes for Perforations (Not Qualifying As FIP) (9)	ELBW (5)
Gastric Perforations: 6	3
Cecal Perforations: 1	1
Duodenal Perforations: 2	1

Clinical Characteristics of Perforations and Clinico-Pathologic Correlations

NEC Group

All the nine babies in the group had universal inflammatory changes throughout the small and large intestines. These babies had a very fast progression of symptoms, tended to be sicker in a shorter span and were unstable pre-operatively. Intra-operative quick lavage with drainage with stomas was mainstay of surgical treatment. More than half of them required two or more operative procedures. Post-operatively these babies had a longer hospital stay. Mortality was higher compared to non-NEC FIP group.

Non-NEC FIP Group

The inflammatory changes were less florid; mostly localized to one segment of bowel usually terminal ileum or cecum / colon or rectum in one instance. There was a large perforation with dehiscence of almost up to one third segment of anti-mesenteric

bowel wall. Despite such large perforation, the infection was rather localized. Interestingly this group was relatively less unstable pre-operatively, did well intra-operatively with resection anastomosis, usually ended without stomas and had a shorter hospital stay. Mortality was lower in this group compared to the NEC group. The authors hence propose a "Theory of Natural Selection" in Non-NEC FIP neonates where in nature localizes the inflammatory process to one segment of bowel over a period of time such that peritoneal processes are able to wall off the perforation preventing generalized sepsis. Timely surgical intervention should predict a reasonably good outcome.

Discussion

Our data show that – during the years 2010 to 2012 – the most frequent surgical emergencies in VLBW infants, NEC and FIP were diagnosed more often in infants with a BW<1250 g compared to those with a higher BW. PS should be able to clinically differentiate groups of patients with clearly distinguished risks for NEC and

FIP and different requirements for surgical interventions. NEC is thought to represent the most frequent emergency in neonatology caused by intestinal disease, and it is commonly assumed that emergencies such as intestinal perforation due to FIP and NEC need immediate intervention by a qualified surgeon (PS). Shorter intervals between the first symptoms, diagnosis, and surgical repair may improve survival, may reduce the need for complex surgical interventions, and may lead to less long-term morbidity, e.g., short bowel syndrome. Early consultation of the neonatologist and the pediatric surgeon may not necessarily result in more surgery; rather, it may result in prolongation of conservative treatment and watchful waiting without missing the appropriate time for surgery [8].

Recently, Linge, et al. [9] have shown that not every preterm infant with gastrointestinal symptoms has FIP or NEC or requires surgery. In 7.9 to 10.8% VLBW infants with BW<1000 g FIP or NEC were diagnosed, but approximately twice that number had shown symptoms which were indicative of these diseases. Thus, 1 in 5 preterm infants with BW<1000 g may need consultation with PS during early stages of acquired gastrointestinal disease. Our data are in accordance with reports in the literature found that NEC incidence in Canada decreased with increasing BW: among infants with a BW between 501 and 1000 g the incidence was 11.2%, compared to 4.3% in infants with a BW between 1001 and 1500 g, and below 2% in infants with a BW above 1500 g. The risk to acquire NEC was nearly doubled in infants with a gestational age <28 weeks compared to those aged 28 weeks and above (odds ratio 1.9; 95% confidence interval 1.4 to 2.7). The data set of the national German reference center for surveillance of nosocomial infection in the years 2008 to 2012 yields a cumulative 5-year NEC incidence of 6% in infants with a BW<500 g (83/1313), of 4.8% in infants with a BW from 500 to 999 g (640/13,220), and of 1.3% in infants with a BW from 1000 to 1499 g (259/30,716) [10]. Thus, both nationally and internationally, published NEC rates are comparable to our data.

To our knowledge, no population-based studies of the epidemiology of FIP in preterm infants have been performed in India. Eicher [11] reported in a single center study on 28 out of 280 preterm infants with a BW<1000 g who underwent surgery for acquired intestinal disease between 2002 and 2007 (19 with FIP, 9 with NEC). In an observational study from Japan, reported on 39 VLBW infants who underwent laparotomy during previous 20 years; 19 of them had NEC, and 8 had FIP. Eicher comment on their FIP rate (6.6% in inborn preterm infants <1000 g BW), which is increased compared to international data, that there may be more awareness regarding the distinction of NEC and FIP, leading to a perceived increase in FIP frequency in more recent studies. Hunter, et al. noticed that, during the past 20 years, there was no significant improvement in mortality and morbidity of VLBW infants related to acquired gastrointestinal disease despite the general progress in neonatal intensive care. Hence strategies must be adopted by Neonatologist to prevent NEC and FIP based on an epidemiologic

analysis. The authors hence propose a “Theory of Natural Selection” in Non-NEC FIP neonates where in nature localizes the inflammatory process to one segment of bowel over a period such that peritoneal processes are able to wall off the perforation preventing generalized sepsis. Timely surgical intervention should predict a reasonably good outcome.

Conclusion

- a) It should be possible to differentiate between NEC perforations and non-NEC FIP depending on clinical characteristics and parameters available. Prospective randomized trials along with histo-pathologic correlation should be done to prove “Theory of Natural Selection” and identify factors for localization of inflammatory changes in non-NEC FIP neonates as compared to NEC neonates thus enabling to predict a favorable outcome for this cohort of neonates.
- b) Strategies must be adopted by Neonatologist to prevent NEC and FIP based on an epidemiologic analysis.
- c) It should be possible to differentiate between NEC perforations and non-NEC FIP depending on clinical characteristics and parameters available.
- d) Timely surgical intervention by PS should predict a reasonably good outcome.
- e) Prospective randomized trials along with histo-pathologic correlation should be done to prove “Theory of Natural Selection” and identify factors for localization of inflammatory changes in non-NEC FIP neonates as compared to NEC neonates thus enabling to predict a favorable outcome for this cohort of neonates.

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