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Risk factors associated with postnecrotizing enterocolitis strictures in infants☆,☆☆

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ABSTRACT

Introduction: Survivors of necrotizing enterocolitis (NEC) often develop a post-NEC intestinal stricture, causing severe and prolonged morbidity.
Objectives: We first aimed to determine the incidence of post-NEC strictures. Second, we aimed to determine risk factors associated with intestinal post-NEC strictures.
Materials and Methods: A total of 441 patients diagnosed with NEC Bell's stage ≥2 were retrospectively included in three academic pediatric surgical centers between January 2005 and January 2013. Clinical data were related to the occurrence of intestinal post-NEC strictures. Post-NEC strictures were defined as clinically relevant strictures with a radiological and/or surgical confirmation of this post-NEC stricture.
Results: The median gestational age of the 337 survivors of the acute phase of NEC was 29 weeks (range 24–41) and median birth weight was 1130 g (range 410–4130). Of the survivors, 37 (17%) medically treated NEC patients developed a post-NEC strictures versus 27 surgically treated NEC patients (24%; $p = 0.001$). Highest C-reactive protein (CRP) level measured during the NEC episode was associated with the development of post-NEC strictures (OR 1.20, 95% confidence interval 1.11–1.32; $p = 0.03$). No post-NEC strictures were detected in patients with CRP levels <46 mg/L.
Conclusion: This multicenter retrospective cohort study demonstrates an overall incidence of clinical relevant post-NEC strictures of 19%, with a higher rate (24%) in NEC cases treated surgically. Increased CRP levels during the NEC episode were associated with the development of post-NEC strictures.

Necrotizing enterocolitis (NEC) is a severe intestinal inflammatory disorder in preterm infants associated with mortality rates reaching 50% in surgical cases [1]. Although many studies have dealt with the possible causes of NEC, less information is available about the development of intestinal post-NEC strictures beyond the acute phase [2].

Since 1978, seven studies are published concerning the development of intestinal post-NEC strictures [3–9]. Survivors of the acute phase of NEC often (up to 40%) develop a post-NEC stricture secondary to a healing process that follows ischemic intestinal injury [3]. The incidence of a post-NEC intestinal stricture is higher after initial surgical treatment (20%–43%) compared to medical treatment (15%–30%) [4–9]. Gaudin and colleagues [3] observed a prodigiously high rate of post-NEC strictures in cases treated surgically (91%). The critical period for the development of post-NEC (symptomatic) strictures is the first 3 months following remission of the acute phase [4]. Post-NEC strictures can lead to severe and prolonged morbidity in the infant because of intestinal obstruction, septicemia, and/or perforation [7–10].

C-reactive protein (CRP) is believed to be the only factor associated with the development of post-NEC strictures [3,11]. However, these results are not yet validated in a larger patient population. Whether other clinical and biological factors are associated with the development of

Abbreviations: AMC, Academic Medical Center; CI, confidence interval; CRP, C-reactive protein; E.C.I., e causa ignota; Hb, hemoglobin; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PNA, postnatal age; SD, standard deviation; UMCG, University Medical Center of Groningen; VUmc, VU Medical Center.

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post-NEC strictures is still unknown. Therefore, the aim of this study was to investigate the incidence- and risk factors for intestinal post-NEC strictures.

1. Materials and methods

1.1. Patients

This multicenter study was conducted at the University Medical Center of Groningen (UMCG), the Academic Medical Center (AMC) in Amsterdam, and the VU Medical Center (VUmc) in Amsterdam. We analyzed patients diagnosed with NEC (Bell's stage ≥ 2) between January 2005 and December 2013 retrospectively. Review of the data collection was approved by the local ethical committee in all three centers.

NEC was confirmed if pneumatosis intestinalis, portal venous gas, or both were present according to the modified Bell's staging criteria [12]. The treatment protocols for NEC followed the national protocol for the management of NEC and did not significantly change between 2005 and 2013. Initial treatment consisted of discontinuation of enteral feeding (days 1–5 nil per os, days 6–8 minimal enteral feeding), nasogastric suction, intravenous administration of broad-spectrum antibiotics (augmentin and gentamicin for 7–10 days), and cardiopulmonary support. Prokinetic drugs and H2-blockers were not used regularly. Indications for surgery included: (1) the presence of an intestinal perforation, and (2) clinical deterioration defined as no recovery despite maximal conservative treatment without the presence of an intestinal perforation. In all operated infants, the surgical protocol used was a laparotomy, including an examination of the entire digestive tract with the search for perforations, resection of frankly necrotic bowel and the construction of a primary anastomosis and/or the creation of a proximal stoma for evacuation. The decision resulting in the construction of a primary anastomosis or the creation of a proximal stoma was all based on the individual situation of the patient (e.g., in case of critically ill patients owing to an intestinal perforation a surgeon would often prefer the placement of a proximal stoma to minimize the operation time) and the individual preference of the surgeon for one of the surgical techniques. We defined the acute phase of NEC as the first 30 days after onset of symptoms.

We defined post-NEC strictures as clinically relevant strictures, based on symptoms that fit with impairment of the passage of contents through the intestine, including the inability to increase the amount of enteral feeding and/or no defecation for >48 hours with the necessity to perform a contrast enema study and/or surgery, all after the acute phase of NEC. When strictures were diagnosed as located on the former anastomotic site, these strictures were assigned as anastomotic strictures, which we did not regard as post-NEC stricture.

1.2. Risk factors for post-NEC strictures

We collected the following patient characteristics from patient reports: gestational age, birth weight, gender, postnatal age at NEC onset, Bell's stage, need for inotropics during the course of NEC, whether surgery was required, and mortality. Furthermore, we collected clinical variables – just before NEC onset and highest value during the acute phase of NEC – including CRP, pH, hemoglobin (Hb), leukocytes, and (lowest) platelet count. The analysis techniques of these laboratory variables were similar in all three institutions with similar references ranges. Additionally, we documented radiography findings derived from the radiology reports, including the presence of pneumatosis intestinalis, an intestinal fixed loop, portal air, and/or intestinal perforation(s). Lastly, data concerning NEC treatment and management were collected, including surgical interventions and complications.

1.3. Data and statistical analysis

We performed a descriptive analysis of all survivors of the acute phase of NEC and a comparative analysis of the group with- and without strictures. All descriptive data are expressed as median (range) or as numbers unless specified otherwise. For testing differences between categorical variables, the χ^2 (chi-square), or Fisher's Exact analysis was used. For testing differences between continuous variables, the Student's t-test or Mann–Whitney U test was used as appropriate. Risk factors for post-NEC strictures were tested both by univariate and multivariate analyses. Statistical analysis was performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics 21, IBM Corp., Armonk, New York, USA). Two sided p-values less than 0.05 were considered statistically significant.

2. Results

The flowchart of the study and the patients' characteristics are shown in Fig. 1 and Table 1, respectively. We included 441 infants, 248 males and 193 females with NEC in this study. A total of 337 (76%) infants survived the acute phase of NEC (<30 days after NEC diagnosis; Fig. 1). Of these survivors median gestational age was 29 weeks (range 24–41) and median birth weight was 1130 g (range 410–4130). Postnatal age at NEC onset was 10 days (range 3–68). Of the survivors 224 (66%) were treated medically during their NEC episode versus 113 (34%) whom were treated surgically. The construction of a temporary proximal stoma of the surgically treated NEC patients occurred in 70 cases (62%) compared to the construction of a primary anastomosis in 43 cases (38%).

In 64 (19%) patients a post-NEC stricture was diagnosed via contrast enema study and/or surgery. In 18 (24%) infants the post-NEC stricture was successfully treated conservatively and in 48 (76%) the post-NEC stricture was treated surgically. Nine infants (8% of the surgically treated NEC infants) developed an anastomotic stricture.

Post-NEC strictures developed in 37 (17%) medically treated NEC patients versus 27 (24%) in surgically treated NEC patients ($p = 0.001$; Fig. 1). Symptoms arose after a median of 27 days (range 16–36) in medically treated NEC patients versus after a median of 51 days (range 22–152) in surgically treated NEC patients ($p = 0.02$). The post-NEC strictures in the medically treated NEC patients were mainly located in the transverse colon and descending colon and in the surgically treated infants in the ascending colon (Table 2).

In children who developed post-NEC strictures we observed higher CRP levels during the course of the disease ($p = 0.009$), lower platelet counts ($p = 0.02$), more often the presence of a fixed loop observed via radiography ($p = 0.02$), and more often surgery during the acute phase of NEC ($p = 0.001$; Table 3). The number of cases in whom surgery was indicated because of clinical deterioration ($p = 0.001$) and in whom a primary anastomosis was constructed, was also higher in children who developed post-NEC strictures ($p = 0.001$; Table 3).

No post-NEC strictures were observed in patients with highest CRP levels under 46 mg/mL during the course of NEC. Highest CRP levels were not associated with severity of disease expressed in Bell's stages ($p = 0.10$). The multivariate analysis showed that highest CRP level during NEC was the only independent risk factor for the development of post-NEC strictures. For each rise in 1 mg/L of highest CRP the risk increased with odds ratio 1.20 (95% confidence interval: 1.11–1.32; $p = 0.03$). For each rise in 10 mg/L of highest CRP the risk further increased with odds ratio 1.47 (95% confidence interval: 1.17–1.78).

3. Discussion

This large multicenter study demonstrates an occurrence rate of 19% of post-NEC strictures in (acute phase) NEC-survivors, with more strictures after initial surgical treatment compared to conservative treatment. The development of post-NEC strictures was significantly