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Necrotizing Enterocolitis

Time to reintroduction of feeding in infants with nonsurgical necrotizing enterocolitis

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ABSTRACT

Background: For infants with necrotizing enterocolitis (NEC) treated nonoperatively, no consensus exists on the optimal fasting period prior to reintroducing feeds after NEC. We report our experience with early (<7 days) and late (≥7 days) refeeding in this population.
Methods: A chart review of infants with NEC born between 2006 and 2016 was performed. Data elements include demographics, comorbidities, day of diagnosis, Bell's stage, recurrence, strictures, length of stay and mortality, and were grouped into early and late refeeding. T-tests were used for means and chi-squared tests for distribution of proportions. Linear and logistic regressions were used to further evaluate the association of length of stay, stricture, recurrence, and death with time to refeeding.
Results: Of 228 NEC patients, 149(65%) were treated nonoperatively (Bell Stages I, IIA, IIB, IIIA). Eleven patients were excluded owing to never restarting feeds, largely secondary to early death. The early (n = 40) and late refeeding (n = 98) groups were not significantly different with regard to mean gestational age at birth, race, birth weight, day of life at NEC diagnosis, or cardiac disease. NEC Stage was significantly different ($p < 0.001$). The late group had significantly more Stage IIB patients ($p = .02$), and the early group had more stage I patients ($p = <0.01$). After adjusting for Bell's stage, the odds of NEC recurrence, death, and the composite outcome of recurrence or stricture or death were not significantly different between early and late groups.
Conclusions: No standardized guidelines exist for restarting enteral nutrition following medical NEC. In patients managed nonoperatively, early reintroduction of feeding was not significantly associated with increased NEC recurrence, mortality, or stricture.
Level of evidence: Treatment Study – Level III.

Necrotizing Enterocolitis (NEC) is the most common cause of emergency surgery in the neonatal intensive care unit (NICU) and carries a mortality rate of up to 30% [1]. Approximately 10% of all NICU deaths are attributed to NEC [2]. Although the exact pathophysiology of NEC remains unclear, potential risk factors have been identified including formula feeding, blood transfusions, aberrant inflammatory signaling, and bacterial colonization [1,3–5]. Very low birth weight (VLBW; <1500 g) premature infants account for >85% of NEC cases, and preventive measures have been employed to reduce the incidence of NEC in this group [4]. These strategies include feeding breast milk rather than formula [6,7], administering probiotics [8–10], and modifying the rate of initial enteral feeds [11–14]. While breast milk feeds have decreased the incidence of NEC in some centers, a number of other clinical variables, including the timing of refeeding after nonsurgical NEC, have been insufficiently studied in the literature.

Because feeding has been associated with the development of NEC, neonatologists and surgeons alike are naturally cautious during the reinitiation of enteral feeds after an episode of nonsurgical NEC. Once the diagnosis of NEC is made, the infant has historically been placed on parenteral nutrition and bowel rest for 7 to 14 days [15,16]. Few studies have addressed the optimization of feeding practices after surviving an episode of NEC [17,18]. The exact duration of bowel rest is usually based on disease severity, need for surgery, and clinical judgment of the neonatologist or pediatric surgeon [19]. However, this common practice of a prolonged fasting period post-NEC is not evidence based. Because there is little definitive evidence to suggest that a prolonged fasting period after nonsurgical NEC, we hypothesized that early refeeding in a patient with NEC treated nonsurgically would not detrimentally affect the major outcomes of stricture, NEC recurrence, or death. In a larger cohort of NEC patients than previously studied, using a retrospective study design, we aimed to discover whether the

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timing of post-NEC feeds adversely affects major clinical outcomes, including NEC recurrence, stricture development, and death, in babies with nonsurgical NEC.

1. Materials and methods

A retrospective chart review was performed at the Medical University of South Carolina, a tertiary care children's hospital with a 64-bed Level IV NICU. Institutional Review Board (IRB) approval was obtained prior to data collection. The clinical data warehouse at MUSC was queried for all neonates discharged from the NICU between 0 and 6 months of age who had a discharge diagnosis of NEC over a 10-year study period from July 2006 to June 2016. ICD-9 and -10 Codes used for the inquiry included 777.5, 777.51, 777.52, 777.53, P77.1, P77.2, P77.3, and P77.9. All data points were entered into a REDCap™ database by three coauthors to maintain consistency. Data points collected included demographic data (age, sex, ethnicity), birth data (mode of delivery, birth weight, gestational age), age (in days) of NEC diagnosis, presence of cardiac disease, Bell's Stage (based on radiographic findings, laboratory data, physical exam findings, and hemodynamics or pressor requirement; Table 1), timing to initiation of feeds and time to goal feeding volume after NEC diagnosis, stricture development, development of recurrent NEC, operative data, and death. Cardiac disease included complex congenital cardiac conditions requiring pediatric cardiac ICU admission, as well as hemodynamically significant patent ductus arteriosus requiring medical or surgical intervention. Data were primarily obtained from the electronic medical record, including daily progress notes and discharge summaries. To study the impact of "early" versus "late" refeeding, patients were then grouped by time to refeeding after NEC, with those starting feeds <7 days after NEC diagnosis considered the "early group," and the patients starting ≥7 days after diagnosis constituting the "late group." This arbitrary time interval was chosen to differentiate infants who had been fed in a more traditional "late" interval (7–14 days) in contrast to those that were fed using more aggressive feeding regimens (less than 7 days). Early and late refeeding groups were analyzed for significant differences in development of stricture, NEC recurrence, and mortality, both individually and as a composite outcome. Secondary outcomes, such as length of stay and the impact of cardiac disease, were also studied.

Descriptive data and univariate analyses were performed for demographic variables and NEC stages by group (proportions, p-values) using STATA (Stata Corporation, College Station, TX). Multivariate logistic regression analysis, adjusted for variables deemed significant with univariate regression, was used to determine the risk of recurrence, stricture, and mortality in each population. Length of stay, a secondary outcome measure, was analyzed with a linear regression analysis model. A p-value of <0.05 was used as the cutoff for statistical significance.

2. Results

We identified 228 patients with a discharge diagnosis of NEC over the 10-year time period. Of the 228 patients who met inclusion criteria, there were 79 (34.6%) operative cases. In addition, there were 11 (4.8%) nonsurgical NEC patients who never restarted feeds after NEC. The remaining 138 (60.5%) were managed nonoperatively, did restart feeds, and were included in the primary analysis. There were 40 infants in the early group (feeds <7 days after NEC) and 98 infants in the late group (≥7 days). The mean gestational age at birth was not significantly different, 30.9 vs 30.3 in early and late groups, respectively. There were no statistically significant differences between groups in terms of race distribution, sex, or presence of cardiac disease (Table 2). The diagnosis of NEC occurred at similar times points in both early (19.0 days) and late (22.6 days) refeeding groups. The majority of patients (>50%) in each group were diagnosed with Bell's stage IIA disease. Significantly more patients in the early refeeding group were diagnosed with Bell's Stage I (42.5% vs. 14.3%, $p < 0.01$), while more patients in the late refeeding group were diagnosed with Bell's Stage IIB disease (2.5% vs 17.3%, $p = 0.02$).

We compared the two refeeding groups for differences in recurrence rates, post-NEC strictures, and death, as well as the composite outcome: post-NEC stricture or recurrence or death. There was no significant difference in mortality between early and late refeeding groups (7.5% vs 8.2%). Recurrence of NEC occurred in two (5.0%) patients in the early group, compared to twelve (12.2%) patients in the late feeding group ($p = 0.20$) (Table 3, Fig. 1). No strictures developed in the early group, but there were four (4.1%) in the late group. There was no statistically significant difference between groups when the incidence of stricture, recurrence, and mortality was combined for composite analysis in a direct comparison (10.0% vs 21.4%, $p = 0.11$).

Using multivariate logistic regression analysis, adjusted for NEC stage at diagnosis, there was no difference in mortality between early and late refeeding groups (Late refeeding odds ratio (OR) 1.29 [95% CI 0.30–5.54]). The analysis was not performed for stricture development, owing to a 0% incidence in the early group. In addition, there was no significant difference in NEC recurrence between the early and late groups on regression analysis (Late refeeding OR 2.91 [95% CI 0.58–14.59]). When the composite outcome was assessed by regression analysis, late refeeding was not significantly different from early refeeding (Late refeeding OR 3.22 [0.95–10.87]).

Length of hospital stay was significantly longer in the late refeeding group regardless of adjustment. Fig. 2 illustrates the strong linear relationship between the length of stay and day of refeeding. Length of hospital stay was much higher in those with cardiac disease noted. In order to separate the effect of cardiac disease from time of refeeding, we performed a subgroup analysis in which patients with cardiac disease were excluded. In those without cardiac disease, length of stay (adjusted for Bell's Stage) was significantly shorter for early refeeding patients on linear regression analysis by 30.5 days [95% CI 9.8–51.2] (Fig. 3).

3. Discussion

There are few data available to guide clinicians in refeeding after nonsurgical NEC. As studies show a recent increase in the incidence of NEC in the United States, a greater emphasis must be placed on evaluation of the broad array of clinical sequelae and outcomes for these patients [4,20,21]. Small, randomized clinical trials have informed neonatologists and surgeons about the surgical management of NEC, but none have addressed optimizing treatment after an episode of nonsurgical NEC [9,22,23]. New information regarding feeding practices

Table 1
Bell's stage used for necrotizing enterocolitis.

Bell's Stage	Vitals/Labs	Radiology	Physical Exam
Stage I	Temp. Instability, Apnea, Bradycardia	Normal gas pattern, Mild ileus	Gastric Residuals, Mild distension
Stage IIA	Temp. Instability, Apnea, Bradycardia	Ileus pattern, Focal pneumatosis, 1 + Dilated loops	Bloody stools, Prominent distension
Stage IIB	Thrombocytopenia, Mild metabolic acidosis	Widespread Pneumatosis, Portal venous gas	Abdominal wall edema/tenderness, Palpable bowel loops
Stage IIIA	Mixed Acidosis, Hypotension, Coagulopathy	Prominent bowel loops, Ascites (without free air)	Severe wall edema, Erythema, Induration Oliguria
Stage IIIB	Shock, Coagulopathy, Severe acidosis	Pneumoperitoneum	Operative Findings: Perforated Bowel

Adapted from Lee and Polin, 2003, Semin in Neonat 2003;8:449–459; Temp = Temperature.