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Early enteral feeding in conservatively managed stage II necrotizing enterocolitis is associated with a reduced risk of catheter-related sepsis

Barbara Brotschi[1], Oskar Baenziger[1], Bernhard Frey[1], Hans Ulrich Bucher[2] and Jörg Ersch[1,*]

[1] Department of Intensive Care and Neonatology, University Children's Hospital, Zurich, Switzerland
[2] Division of Neonatology, Department of Obstetrics and Gynecology, University Hospital Zurich, Switzerland

Abstract

Aims: To compare the effect of fasting period duration on complication rates in neonates managed conservatively for necrotizing enterocolitis (NEC) Bell stage II.
Methods: We conducted a multicenter study to analyze retrospectively multiple data collected by standardized questionnaire on all admissions for NEC between January 2000 and December 2006. NEC was staged using modified Bell criteria. We divided the conservatively managed neonates with NEC Bell stage II into two groups (those fasted for <5 days and those fasted for >5 days) and compared the complication rates.
Results: Of the 47 conservatively managed neonates Bell stage II, 30 (64%) fasted for <5 days (range 1–4 days) and 17 (36%) for >5 days (range 6–16 days). There were no significant differences for any of the patient characteristics analyzed. One (3%) and four (24%) neonates, respectively, developed post-NEC bowel stricture. One (3%) and two neonates (12%) suffered NEC relapse. None and five (29%) neonates developed catheter-related sepsis.
Conclusion: Shorter fasting after NEC appears to lower morbidity after the acute phase of the disease. In particular, shorter-fasted neonates have significantly less catheter-related sepsis. We found no benefit in longer fasting.

Keywords: Catheter-related sepsis; intestinal stricture; necrotizing enterocolitis (NEC); neonate; nutrition.

*Corresponding author:
Jörg Ersch, MD
Department of Intensive Care and Neonatology
University Children's Hospital
Steinwiesstr. 75
CH-8032 Zurich
Switzerland
Tel.: +41 44 266 70 76
Fax: +41 44 266 71 68
E-mail: joerg.ersch@kispi.uzh.ch

Introduction

Necrotizing enterocolitis (NEC) is the most common acquired intraabdominal emergency in infants [10] and the most common surgical emergency in the neonatal intensive care unit (NICU) [11]. Incidences range from 3% to 28%, averaging 6%–10% in infants with birth weights <1500 g, and incurring a mortality of 10%–30% [7]. Although the precise cause remains unclear, incriminated factors include impaired immunity of the immature gut, enteral feeding, and bacterial gut colonization, although no specific pathogen has been identified [12, 16].

Treatment of sonographically and radiologically confirmed NEC consists of nasogastric decompression, antibiotic therapy, total parenteral nutrition (TPN), and surgery when necessary. There is no standard recommendation for when to reinitiate enteral feeding in nonsurgically treated infants. Textbooks recommend resting the bowel for 7–10 days [3, 7]. However, the scientific basis for relatively prolonged fasting is unclear [13]. The issue of fasting period duration is particularly important in a NICU such as ours that manages most of its NEC cases conservatively. We therefore conducted a multicenter comparison of fasting period duration in conservatively managed NEC Bell stage II to determine its effect on complications such as bowel stricture, NEC relapse, and catheter-related sepsis.

Patients and methods

We conducted a retrospective analysis of all term and preterm neonates with NEC ($n=124$) admitted to five Swiss NICUs between January 2000 and December 2006. All NICUs were tertiary centers, well equipped for managing sick neonates with pediatric surgical support. We used data collected by standardized questionnaire. Three NICU questionnaires were filled out by the same person in the study group and the other two by a NICU neonatologist. The questionnaires incorporated the international definition of NEC and the Bell stages [2]. They covered the following items: fasting period duration (some NICUs followed a fixed 5-day regime, others a fixed 10-day regime, but all often tailored the period according to their individual experience [fasting period range: 4–14 days] and modified Bell criteria [8]); gestational age; birth weight; sex; antenatal steroids; cause of prematurity; umbilical catheterization; patent ductus arterio-

sus; initial ventilatory support; surfactant replacement; indomethacin therapy; and concomitant disease (bronchopulmonary dysplasia, retinopathy of prematurity, intraventricular hemorrhage (IVH), and periventricular leukomalacia). Retinopathy of prematurity and IVH were defined as significant if >grade II [9–11, 15, 17, 20]. Patent ductus arteriosus based on echocardiologic criteria qualified only if it required treatment (indomethacin or surgery). Diagnostic data for NEC related to clinical signs, cultures (blood and stool), and imaging (X-ray). Therapy and complication variables included circulatory and/or ventilatory support during the acute phase of NEC, surgery versus conservative management, antibiotic therapy, TPN duration, short bowel syndrome, bowel stricture (defined as significant if suspected clinically, confirmed radiographically and requiring surgery in the neonatal period), NEC relapse, and catheter-related sepsis. Catheter-related sepsis was diagnosed using the Centers for Disease Control criteria: clinical signs of sepsis, one positive peripheral blood culture, and negative urine and tracheal aspirate cultures [14].

All neonates included in Bell stage II showed the same classical clinical and radiologic signs. For that reason all neonates with radiologic pneumatosis intestinalis and/or portal venous gas were staged Bell II. Neonates with metabolic acidosis (pH<7.2), receiving inotropes or mechanical ventilation were staged Bell III. The retrospective design made subtle distinction between Bell stages IIa and IIb impossible.

Since conservatively managed neonates in Bell stage II were our primary focus, we subdivided the infants concerned into those fasted for <5 days and those fasted for >5 days to permit comparison of complication rates, primarily bowel stricture, NEC relapse, and catheter-related sepsis. We chose the 5-day cutoff because it was half the duration of the longest standard regime (10 days) in any NICU. We focused on neonates in Bell stage II, because the criteria of Bell stage I (suspected NEC) are quite vague, with the potential for inconsistent reporting and classification. We also excluded Bell stage III neonates because all required surgery.

After different fasting periods in the individual NICUs, the same feeding algorithm was implemented. It comprised 10 mL/kg body weight (BW) solution by gastric tube in 12 or 8 portions/d on day 1 (D1), 10 mL/kg BW breast milk or formula milk on D2, increasing by 20 mL/kg BW/d to 140–150 mL/kg BW/d.

Statistical analysis: we analyzed normally distributed continuous variables using the unpaired *t*-test and categorical variables using Fisher's exact test.

Results

The total population of 124 infants with Bell stage I–III NEC included five term and 119 preterm neonates (<32 weeks, n=89; ≥32 weeks, n=30). Over the 7-year study period, the five NICUs admitted 2005 inborn preterm neonates aged <32 weeks, giving an incidence of NEC of 4.4% in this age group. Treatment was conser-

Table 1 Patient characteristics (n=124).

	Therapy		
	Conservative Bell I and II	Surgical Bell III	P-value
Patients, n (%)	75 (60)	49 (40)	
Female	34 (45)	23 (47)	0.85
Male	41 (55)	26 (53)	0.85
Gestational age, weeks (mean±1 SD)	31.4±2.8	28.9±3.4	<0.0001
Birth weight			
g (mean±1 SD)	1519±540	1151±541	0.0003
<10th percentile, n (%)	12 (16)	4 (8)	0.28
Cesarean section, n (%)	69 (92)	40 (81)	0.1
Antenatal steroids, n (%)	54 (72)	35 (71)	>0.99
Maternal disease, n (%)			
Preeclampsia	15 (20)	13 (27)	0.5
Amniotic infection	15 (20)	10 (20)	>0.99
Placental abruption	8 (11)	10 (20)	0.19
Catheter, n (%)			
Umbilical venous	11 (15)	17 (35)	0.009
Umbilical arterial	23 (31)	20 (41)	0.56
Initial respiratory support, n (%)			
Ventilator	23 (31)	23 (47)	0.06
NCPAP	22 (29)	16 (33)	0.84
Surfactant therapy	25 (33)	20 (41)	0.35
Bronchopulmonary dysplasia, n (%)	5 (7)	5 (10)	0.51
Patent ductus arteriosus, n (%)	10 (13)	19 (39)	0.002
Indomethacin therapy, n (%)	10 (13)	17 (35)	0.008
IVH >grade II, n (%)	3 (4)	6 (12)	0.16
Retinopathy of prematurity >grade II, n (%)	0 (0)	1 (1)	0.4

n=number, SD=standard deviation, NCPAP=nasal continuous positive airways pressure, IVH=intraventricular hemorrhage.

vative in 75/124 neonates (60.5%) and surgical in 49 (39.5%). Surgically treated neonates were more seriously ill and of lower gestational age (Table 1).

Of the 75 conservatively managed neonates, 28 (37%) were classified as Bell stage I and 47 (63%) as Bell stage II. Of the neonates classified as Bell stage II, 30 (64%) fasted for <5 days (range 1–5 days; NICU1 n=28, NICU2 n=2, NICU3–5 n=0) and 17 (36%) for >5 days (range 6–16 days; NICU1 n=3, NICU2 n=7, NICU3 n=4, NICU4 n=3, NICU5 n=0). All were preterm except for two and one neonates, respectively. Characteristics of the groups did not differ (Table 2) except for "blood in stool", which was less frequent in neonates with fasting period >5 days (P=0.0003). Ages at NEC symptom onset (mean, SD) were 8.6±7.8 and 9.4±9.0 days (P=0.74). TPN was administered for 14.9±4.0 and 18.5±5.9 days (P=0.02). Neonates in the <5 days group needed 14.9±4.0 (range 8–25) days of fasting until initiation of full enteral nutrition vs. 18.5±5.9 (range 10–36) days needed by those in the >5 days group (P=0.02).

Complications (Table 3)

None and five neonates (29%; NICU1 n=1, NICU2 n=2, NICU3 n=2, NICU4/5 n=0) developed catheter-related sepsis, a single episode in all cases (P=0.004). Blood cultures yielded coagulase-negative Staphylococcus (n=5). One (3%) and four neonates (24%) required surgery for early post-NEC stricture (P=0.05); all had evidence of ileus with vomiting, abdominal distension, and confirmatory radiology. One (3%) and two neonates

Table 3 Complications in conservatively managed necrotizing enterocolitis Bell stage II.

	Fasting period		
	<5 days	>5 days	P-value
Catheter-related sepsis, n (%)	0	5 (29)	0.004
Early post-NEC stricture, n (%)	1 (3)	4 (24)	0.05
NEC relapse, n (%)	1 (3)	2 (12)	0.27

n=number, NEC=necrotizing enterocolitis.

Table 2 Patient characteristics of conservatively managed necrotizing enterocolitis Bell stage II.

	Fasting period		
	<5 days	>5 days	P-value
Patients, n (%)	30 (64)	17 (36)	
Female	12 (40)	7 (41)	>0.999
Male	18 (60)	10 (59)	>0.999
Gestational age, weeks (mean±1 SD)	32.0±2.8	31.7±3.0	0.77
Birth weight			
g (mean±1 SD)	1717±560	1545±535	0.3
<10th percentile, n (%)	3 (10)	0	0.29
Cesarean section, n (%)	28 (93)	16 (94)	>0.999
Antenatal steroids, n (%)	24 (80)	12 (71)	0.49
Maternal disease, n (%)			
Preeclampsia	5 (17)	5 (29)	0.46
Amniotic infection	6 (20)	4 (24)	>0.999
Placental abruption	5 (17)	2 (12)	>0.999
Initial respiratory support, n (%)			
Ventilator	8 (27)	6 (35)	0.74
NCPAP	8 (27)	4 (24)	>0.999
Surfactant therapy	7 (23)	5 (29)	0.73
Bronchopulmonary dysplasia, n (%)	1 (3)	1 (6)	>0.999
Catheter, n (%)			
Umbilical venous	4 (13)	3 (18)	0.68
Umbilical arterial	9 (30)	6 (35)	0.75
Patent ductus arteriosus, n (%)	5 (17)	2 (12)	>0.999
Indomethacin therapy, n (%)	5 (17)	2 (12)	>0.999
IVH >grade II, n (%)	1 (3)	0	>0.999
Retinopathy of prematurity >grade II, n (%)	1 (3)	1 (6)	>0.999
Age at NEC onset, days (mean±1 SD)	8.6±7.8	9.4±9.0	0.74
Positive blood cultures at NEC diagnosis, n (%)	2 (7)	3 (18)	0.34
Blood in stool, n (%)	30 (100)	10 (59)	0.0003
Pneumatosis intestinalis, n (%)	30 (100)	17 (100)	>0.999
TPN administered, days (mean±1 SD)	14.9±4.0	18.5±5.9	0.02

n=number, NCPAP=nasal continuous positive airways pressure, NEC=necrotizing enterocolitis, SD=standard deviation, IVH=intraventricular hemorrhage, TPN=total parenteral nutrition.

(12%) relapsed (P = 0.27), with symptom onset ranging from 3 to 4 weeks after the initial episode; one was treated conservatively, the other two surgically. Stricture and relapse rates tended to be lower in the shorter-fasted group. No neonate developed short bowel syndrome and none died.

Discussion

Despite many studies of enteral feeding before the onset of NEC [18], data are lacking on the timing of enteral re-feeding after NEC, hence the absence of consensus guidelines. A 1975 report associated relapse in "several patients" with the reintroduction of enteral feeding <10 days after NEC [8]. Textbooks offer the unsubstantiated recommendation to rest the bowel for 7–10 days [3, 7]. However, a 2003 study concluded that early enteral feeding after NEC was associated with significant benefits and no apparent adverse effects [5]. Early re-feeding may have a healing effect or, at least, helps recovery of the intestinal mucosa. Local trophic nutrients support and stimulate mucosal growth and may thus be protective. In contrast, in the absence of enteral feeding, mucosal villous atrophy may occur within one week, predisposing to recurrent intestinal injury and feeding intolerance [4, 12].

Our analysis of five Swiss neonatal units mirrors the variability in the literature over post-NEC re-feeding. Although each unit practices the same re-feeding regime, they differ in their belief as to when re-feeding should start, in particular, in conservatively managed stage II NEC. Whereas one unit has already managed to significantly shorten the fasting period, the other units, despite the same severity of NEC, are still equivocal over the introduction of advanced re-feeding. Individual experience is still much too often at work. This raises the questions: When is the right time to re-feed in stage II NEC and are long fasting periods actually counterproductive?

Our retrospective study shows that early enteral feeding in conservatively managed NEC stage II is associated with less catheter-related sepsis, which may be related to the shorter requirement for TPN, but our data also reveal no adverse effects of shorter fasting. On the contrary, the rates of bowel stricture (3% vs. 24%) showed only borderline significance and relapse (3% vs. 12%) tended to be lower than in longer-fasted neonates. Assuming an NEC relapse rate of roughly 6% (for conservatively managed neonates) in this study, 356 patients would be required per treatment arm to have a modest chance of detecting a doubling of the NEC relapse rate (80% power, at 0.05 significance level). With only 17 patients in one of the treatment arms, this study was underpowered for detecting this clinically important outcome (it was only powered to detect a difference in relapse rates of 6% vs. 45%).

Early stricture, within the neonatal period, is quite a common complication of NEC. It occurs in conservatively managed neonates as well as in those treated surgically, and is presumably due to post-ischemic scarring [1]. Treatment is always surgical. No specific (including bacteriological) criteria have succeeded in predicting which patients are at risk of stricture after conservative management [6]. The incidences in our study, namely 3% and 24%, were somewhat lower than the 16%–37% reported in the literature [6, 19].

The incidence of NEC in our overall population of preterm neonates <32 weeks, 4.4%, was within the reported range [3, 7, 12]. Similarly, our relapse rates in conservatively managed neonates, 3% and 12%, were also consistent with the literature [3, 9] despite potential inconsistencies in reporting this parameter: The five NICUs differed in their interpretation of certain signs (e.g., blood in the stool), and did not always classify them as relapse.

Despite our study's limitations, e.g., its retrospective design, our observations suggest that early enteral feeding after conservatively managed NEC stage II may lower morbidity after the acute phase of the disease. In particular, neonates fasting for a shorter period had significantly less catheter-related sepsis. We failed to identify any benefit in longer fasting.

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