TITLE PAGE

Title:

Association between timing of re-introduction of enteral feeding and short-term outcomes following laparotomy for Necrotising Enterocolitis

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Declarations of Interest:

None

ABSTRACT

Purpose

To investigate the relationship between timing of re-introduction of feeds following surgery for Necrotising Enterocolitis (NEC) and important early outcomes

Methods

Secondary analysis of prospectively collected data from paediatric surgical units in UK/Ireland of infants who underwent laparotomy for NEC between 01/03/2013 and 28/02/2014. Multivariable logistic regression analysis was used to compare the relationship of early (≤7 days) and later (8-27 days) re-introduction of feeding after surgery on death or need for PN at 28 days, correcting for known cofounders.

Results:

41/143 infants (29%) received early and 102/143 infants (71%) had delayed reintroduction of feeding. Infants in the early feeding group had a higher gestational age at birth, higher proportion of growth restriction, lower inotrope requirement, and weremore likely to have undergone primary anastomosis. Following adjustment there was no statistically significant difference detected in the rate of death or need for PN at 28 days, adjusted OR 0.4 (95% CI 0.2-1.1), noting the limited statistical power of this comparison.

Conclusions:

There is no evidence from this study to support a minimum period of 7 days nil by mouth post laparotomy for infants with NEC. Early feed reintroduction following laparotomy for NEC is safe in appropriate cases.

Key Words: Neonatal, Necrotising Enterocolitis (NEC), bowel rest, treatment, Total Parenteral Nutrition (TPN)

Level of Evidence: Level II – Treatment Study Group; Prospective comparative study

1. **INTRODUCTION**

1.1 **Background**

Since the late 1970s, the mainstays of necrotizing enterocolitis (NEC) management have been nasogastric decompression, bowel rest, antibiotics, intravenous fluid resuscitation, and total parental nutrition (PN) [1-8]. Bowel rest is proposed as a method for allowing resolution of the intestinal inflammation that is the basis of NEC development and propagation. However, the optimal management of infants with NEC remains unclear, and mortality rates, particularly for those infants who require surgery, remain high [3-5]. There is increasing evidence that prolonged bowel rest may actually be detrimental to these infant due to the importance of enteral feeding for development of the intestinal immune system, bowel motility, the mucosal epithelium and gastrointestinal enzyme and hormone production in the premature neonate [9-17] coupled with the risks of prolonged use of PN use; including sepsis, liver failure, and the risks associated with central venous catheter insertion [18-20]. Whilst most clinicians therefore agree that treatment of NEC requires infants to be kept 'nil by mouth' for a period of time, there is uncertainty as to how long this period of time should be. A period of 7 to 14 days bowel rest is commonly quoted as standard practice [4-6], however, wide variation exists, and many clinicians now rest the bowel for as little as 72 hours post diagnosis [9, 19-25]. Though three previous studies have investigated outcomes of early versus delayed feeding post diagnosis of medically managed NEC; none has reported outcomes with early or delayed feeding regimes in infants primarily with advanced NEC requiring surgery [22-25].

List of Abbreviations: *NEC - Necrotising Enterocolitis, PN - Parenteral Nutrition, SIP - Spontaneous Intestinal Perforation, SGA - Small of Gestinational Age, IQR - Interquartile Range, OR - Odds Ratio, PNALD - Parenteral Nutrition Association Liver Disease.*

1.2 **Aims**

The specific aims of this study were to:

1. Describe the variation in duration of intestinal rest in infants in the UK/Ireland with laparotomy confirmed NEC; and
2. Investigate whether early (≤7 days following decision for laparotomy) compared with later (8-27 days) re-introduction of feeds was associated with variation in the rate of PN use or death at 28 days post-surgical intervention.

2. MATERIALS AND METHODS

2.1 Summary

We undertook a secondary analysis of a prospectively collected dataset of all infants in the UK and Ireland who underwent laparotomy for NEC between 01/03/2013 and 28/02/2014, and who survived to re-introduction of feeds. Collection of data that formed the original dataset received ethical approval (UK REC:12/SC/0416).

2.2 Data collection

In the original cohort study [21], cases were identified via monthly reporting cards sent to lead clinicians at participating centres, with detailed data collection forms completed in response to notification of a case. All data were anonymous, and double entered into a customised database. Duplicates were excluded by comparing reporting hospital, mother's year of birth, and date of first operation. If any data items were missing, or fell outside pre-specified ranges, clinicians were contacted to obtain the required information.

2.3 Inclusion Criteria

Infants were eligible for inclusion in this study if they were diagnosed with NEC on visual inspection of the bowel at the time of a laparotomy. Infants who were presumed to have NEC, but never underwent laparotomy or subsequently diagnosed with spontaneous intestinal perforation (SIP) at the time of laparotomy were excluded from the study. Infants who had not re-started feeds within 28 days of laparotomy were excluded from the analysis. This was because introduction of feeds after 28 days post-surgery would prevent establishment of a temporal relationship between re-introduction of feeds and the outcomes of interest; which were measured at 28 days post-surgery.

2.4 Outcomes

The primary outcome was a composite of death prior to 28 days post-surgical intervention, and ongoing need for PN at 28 days post-surgical intervention. The requirement for PN at 28 days has been previously shown to be an independent predictor of one-year mortality and is probably surrogate for other clinically important outcomes including PN usage, time spent with a central venous catheter, catheter related sep-

sis and PN associated liver disease (PNALD) [19,21]. Death prior to 28 days was included in the composite with PN use at 28 days, as infants who died prior to 28 days could by default not be on parenteral nutrition at 28 days. Therefore, if death were not included in the composite, a low rate of parenteral nutrition use in one group could potentially have been explained by a high mortality rate in that same group, thereby making data interpretation challenging.

2.5 **Feeding Group Definitions**

The date on which feeds were re-introduced was defined as per the reporting surgeon. No stipulation was made as to volume or type of enteral feed that must have been given in order for an infant to be defined as having re-started enteral feeding. We considered that infants within lowest quartile for time to re-introduction of feeds could be considered to have 'early' reintroduction of feeds. As the median time to re-introduction in this cohort was 10 days (interquartile range of 7-13days), we defined this as ≤7 days. This definition aligns well with accepted standard practice for bowel rest for infants with NEC [4-6].

3.0 **CALCULATION**

Baseline characteristics of infants in each feeding group were described using descriptive statistics. Proportions of infants who had died prior to 28 days of age, or who required parenteral nutrition at 28 days of age were calculated based upon the number with returned data.

Characteristics of infants in the early (≤7 days) and delayed (8-27 days) feeding groups were compared using the Chi^2 test of significance. Unadjusted, univariate logistic regression analysis, and multivariate logistic regression analysis adjusted for gestational age at birth, birthweight less than 10^{th} centile for gestational age (small for gestational age – SGA), and disease severity (assessed by inotrope requirement at surgery, and operation performed) were used to investigate the relationship between early (≤7 days) re-introduction of feeds and death or need for PN at 28 days. These characteristics were adjusted for as they have previously been shown to be associated with outcome in infants with NEC [27]. Sensitivity analysis was carried out with infants who restarted feeds from 21-28 days to test for any bias created within the need for PN at 28 days outcome.

4. **RESULTS**

4.1 **Infant characteristics**

Of 236 infants in the original cohort study [19], 143 (61%) met the inclusion criteria for this secondary analysis. Reasons for non-inclusion were: no definite laparotomy confirmed diagnosis of NEC (n=47, 20%); feeds not restarted prior to 28 days (n=20, 11%); and timing of feed initiation unknown (n=26, 14%). Therefore, of the 189 infants with laparotomy confirmed NEC, 143 (76%) were included in this secondary analysis (Figure 1).

Those infants with laparotomy confirmed NEC who were excluded from the analysis were more likely than those who were included in the analysis to have an additional congenital anomaly, to have abdominal wall erythema or discolouration at presentation, and to require inotropes at the time of surgery (Table 1).

Of the 143 infants in the cohort 41 (29%) restarted feeds within the first 7 days of surgery and 102 (71%) between 8 and 27 days after surgical intervention. The median time (IQR) to restarting feeds was 6 days (range: 5-6 days) and 11 days (range: 10-14 days) in the early and late feeding groups respectively. Infants in the early feeding group were of greater gestational age at birth than those in the delayed feeding group, but were also more likely to be small for gestational age at birth than those in the delayed feeding group (Table 2). Infants in the early feeding group were also less likely to require inotropes at the time of surgery than those in the delayed feeding group, and more likely to have undergone resection and primary anastomosis (Table 2). There were no other statistically significant differences in baseline characteristics between the two feeding groups.

4.2 **Outcomes**

In the early feeding group (n=41) there were two infants (5%) who died prior to 28 days post-surgical intervention, 14 infants (34%) who required PN at 28 days post-surgical intervention, and one infant (2%) in whom it was not known at what point their parenteral nutrition was stopped. In the late feeding group (n=102) there were two infants (2%) who died prior to 28 days post-surgical intervention, and 65 (64%) who required PN at 28 days (Table 3). Thus the combined primary outcome was less frequent in the early feeds group compared to the late feeds group. Following adjustment for the *a priori* specified covariates, there was no statistically significant as-

sociation between feeding group and the composite outcome of need for PN or death at 28 days, adjusted OR 0.4 (95% CI 0.2-1.1,p=0.07) (Table 4). There were six infants who restarted feeds between 21 and 27 days, however, sensitivity analysis with these infants excluded produced a negligible difference to the adjusted Odds of death or needing PN at 28 days (0.5, 95% CI 0.2-1.2 p=0.123).

5. **DISCUSSION**

This analysis has characterised current practice in relation to timing of initiating feeding after surgical intervention for infants with laparotomy confirmed NEC. The majority (54%) of the 189 infants included started enteral feeding between eight and 27 days with only 22% and 11% starting enteral nutrition within seven days and after 28 days respectively. Those infants in whom enteral nutrition was started within seven days appeared to be less severely unwell (lower inotrope requirement) and were of greater gestational age at birth than those who were known to have restarted enteral nutrition between eight and 27 days. Following adjustment for the *a priori* specified confounding factors, there was no statistically significant association (p=0.07) between timing of feed re-introduction and death or need for PN at 28 days. However, the limited power of this analysis to detect what may be a clinically important difference as statistically significantly different must be recognised.

The strengths of this study are three-fold. Firstly, it is the first population-based description of feeding strategies on a country-wide level. Secondly, the use of laparotomy confirmation of NEC has allowed for a robust definition of the condition, and so a more homogeneous cohort, thereby removing the diagnostic ambiguity that is a cause for concern in studies of medically managed NEC [23-25]. Lastly, robust analysis with adjustment for appropriate cofounders was possible due to the detailed, prospective data collection methodology which ascertained specific feed timings and differences in demographics between the different feeding groups.

The major limitation of the study is that despite collection of national data over a year-long period, the studied cohort remains relatively small due to the low incidence of surgically managed NEC, the use of a robust definition of NEC and complete data availability. By limiting surgically defined NEC only we have potentially excluded infants with more severe NEC, i.e. those who were excluded because they restarted feeds after 28 days, or because they died prior to undergoing a laparotomy. Despite this the cohort of 143 infants described here is still larger than the three previous studies to date. [23-25]. These also focused on low grade NEC; one study including

Bell's stage II only and the largest study including Bell's stage I patients with exclusion above stage III [24,25]. Our study therefore likely represents the most reliable comparison of these two management strategies currently available.

This work is also likely to be affected by limitations that are common to many non-randomised studies, including confounding by intention; surgeons appear to be re-starting feeds earlier in infants with less severe NEC, or those with less co-morbidities. In order to account for these differences in baseline demographics and disease severity, we have adjusted for known confounding factors. However, it is likely that cofounders that we cannot correct for, in particular variations in feed practice such as type and rate of feed re-introduction, and other unknown factors may also be affecting the relationship between timing of feed reintroduction and death or need for PN at 28 days.

To our knowledge, this is the first study to investigate the effect of time to re-initiation of feeding on outcome in a robustly defined cohort of infants with ***surgically*** managed NEC. A meta-analysis of time to re-initiation of enteral feeding following treatment for ***either*** surgically or medically managed NEC [22] identified only three studies, all comparing early and late feeding regimens that were heterogenous in their definitions [23-25]. One of these studies, conducted in a single centre, compared a new initiative for early feeding after three consecutive days without evidence of NEC (as defined by absence of portal venous gas on ultrasound) against historical data where feeds were re-initiated at the neonatologists discretion [23]. The second study used more specific definitions, separating infants into early (<5 days) and late (> 5 days) re-initiation of enteral feeds, and included infants from 5 neonatal units [24]. Both of these studies were small with a combined total of 91 patients, of which 83.5% (n=76) were medically managed. The most recent study looked at 10 years of retrospectively collected data from a single centre and included 138 neonates with Bell's Stage III or lower NEC, with exclusion of surgically managed infants [25]. Although none used an identical outcome to that in the present study, all reiterate the current findings and reported significant benefits from early feed re-introduction including reduced need for PN and fewer days with a central venous catheter [19-21]. The meta-analysis showed reduced rates of NEC recurrence (5 vs 12%), stricture rate (0 vs % and mortality (7.5 vs 8.2%) in the early feeding group though no result was significant [22]. These results go against the hypothesis that early re-introduction of feeds in infants with NEC results in worse outcomes because it may lead to propogation of the underlying inflammatory process. There are several mechanisms that potentially ex-

plain this finding. Firstly, the intestinal mucosa gains the majority of its nutrients from the bowel lumen, and the removal of enteral feeding has been shown to result in impairment of the epithelial barrier function and thus potentially increasing the risk of bacterial translocation and sepsis [10,26]. Secondly, the make-up of the gut microbiome has been recognized to be important in the development of NEC and the subsequent course of the disease [11,27]. Enteral feeds maintain a healthy gut microbiome equilibrium. Finally, early re-introduction of enteral feeding allows earlier cessation of PN and therefore removal of central venous catheters. Risk of central line associated infections is thereby reduced.

6. CONCLUSION

These data suggest no detrimental affect to restarting enteral feeding before the conventionally accepted 7 days in appropriate selected cases. However, a suitably powered randomized controlled trial, or addition of similarly high quality population-based observational data in a robustly defined population with surgical NEC is necessary to provide more definitive evidence. Such studies should also report data from longer-term outcomes, other outcomes of importance, including recurrence of NEC, and more general neonatal outcomes, including those identified by the core outcomes in neonatology (COIN) study [27].

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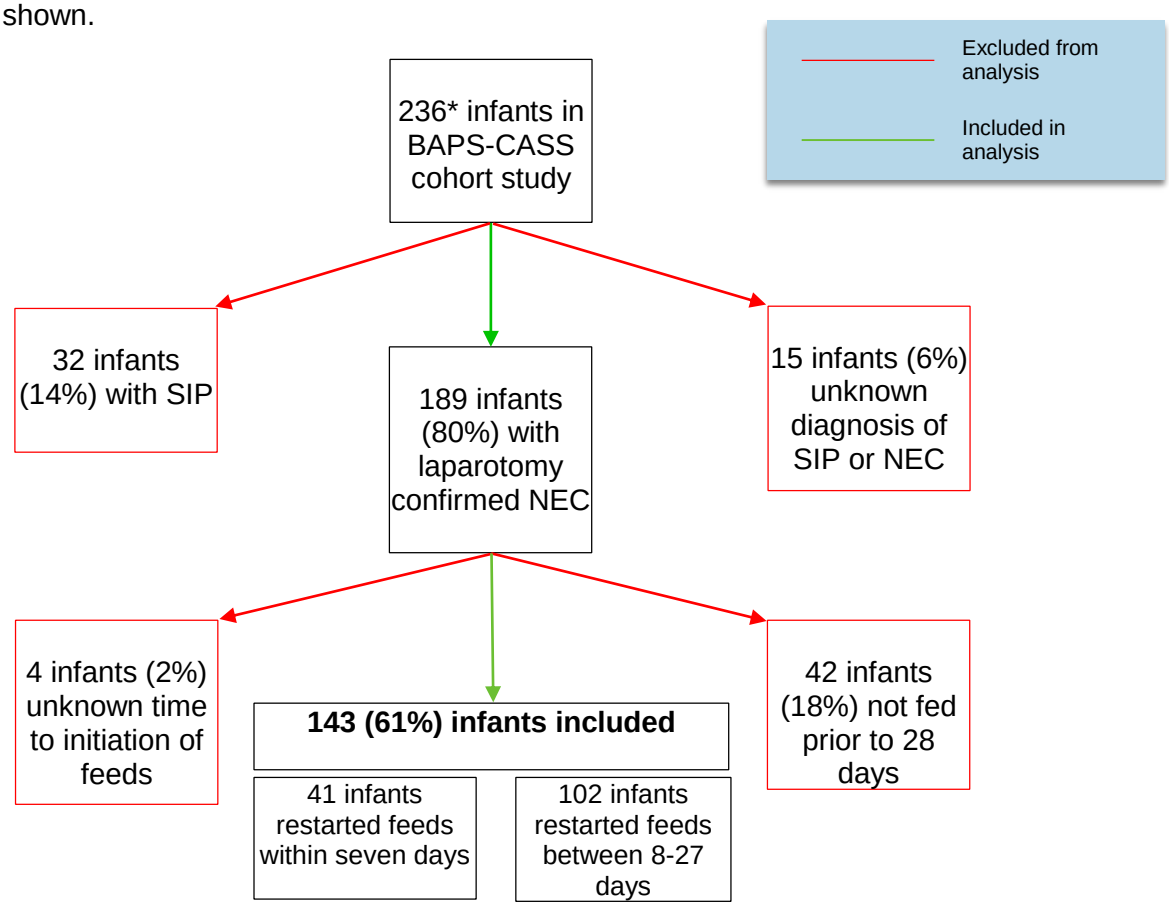
Figure 1: Flow diagram of patient selection and exclusion with numbers and reason for patient drop out shown.



* Percentages expressed are of the total number of infants in the BAPS-CASS cohort (236)

Table 1: Baseline characteristics of the included and excluded infants with differences expressed as p-values.

		Excluded from Analysis	Included in Analysis	p-value
		Restarted feeds after 28 days, or time to initiation of feeds unknown	Timing of initiation of feeds known	
Total Patients		N=46	N=143	
Ethnicity	**Black or Asian Minority Ethnicity**	24 (60%)	58 (42.6%)	0.053
	White British	16 (40.0%)	78 (57.4%)	
Small for Gestational Age	**No**	37 (82.2%)	123 (86.6%)	0.46
	Yes	8 (17.8%)	19 (13.4%)	
Sex	**Female**	16 (34.8%)	60 (42.0%)	0.39
	Male	30 (65.2%)	83 (58.0%)	
PDA Ligation Performed	**No**	43 (95.6%)	133 (93.0%)	0.54
	Yes	2 (4.4%)	10 (7.0%)	
Non-cardiac congenial anomaly	**No**	35 (77.8%)	132 (92.3%)	0.007
	Yes	10 (22.2%)	11 (7.7%)	
Abdominal wall erythema or discolouration at presentation	**No**	26 (56.5%)	107 (74.8%)	0.018
	Yes	20 (43.5%)	36 (25.2%)	
Inotropes required at time of surgery	**No**	19 (41.3%)	97 (68.3%)	0.001
	Yes	27 (58.7%)	45 (31.7%)	

Table 2: Comparison of known cofounders between the early and delayed feeding groups

Baseline Characteristics	Early Feeding Group (</=7 days post intervention) N=41 (29%)	Delayed Feeding Group (>7 days post intervention) N=102 (71%)	p value
Median (IQR) gestational age at birth (completed weeks)	27 (25-32)	26 (25-29)	0.04
Median (IQR) birth weight (grams)	1045 (728-1698)	938 (761-1291)	0.1
Small for gestational age (<10th centile)	11 (27%)	9 (9%)	0.007
Non-cardiac congenial anomaly	6 (15%)	6 (6%)	0.1
Inotropes given at time of surgery	8 (20%)	37 (36%)	0.04
Resection and Primary Anastomosis	17 (41%)	11 (11%)	<0.001
Resection and Stoma Formation	19 (46%)	68 (67%)	<0.001

**Data for other operations performed has not been published, as the low number of infants in individual categories would render those infants potentially identifiable.*

Table 3: Outcomes in the early and delayed feeding groups

Outcome	Early feeding N=41	Delayed Feeding N=102
	n (%)	n (%)
Died prior to 28 days	2 (5%)	2 (2%)
Required PN at 28 days	14 (34%)	65 (64%)
Missing data regarding PN use at 28 days	1 (2%)	0 (0%)
Alive and not requiring parenteral nutrition at 28 days	24 (59%)	35 (34%)

*Percentages expressed are the proportion of the total within each group.

Table 4: Unadjusted and adjusted primary outcome analysis across the two groups.

		Early Feeding N=41 n(%)*	Delayed feeding N=102 n(%)*	OR (95% CI) p value	Adjusted~ OR (95% CI) p value
Died prior to or still requiring PN at 28 days	Yes	16 (40%)	67 (66%)	0.3 (0.2-0.8), p=0.005	0.4 (95% CI 0.2-1.1,p=0.07).
	No	24 (60%)	35 (34%)		

*Percentage of those with complete data for outcome

~ Adjusted for the a priori specified covariates of gestational age at birth, small for gestational age, inotrope requirement at surgery, and operation performed

Highlights;

- First population-based description of feeding strategies of surgically managed NEC on a country-wide level.
- Most infants have feed re-introduced between 8 and 28 days after surgery, but one fifth re-start feeds at 7 days or less
- Re-introduction of feeds at 7 days or less is not associated with worse outcome at 28 days