


# Do more mature preterm babies with surgical necrotizing enterocolitis predominantly develop the colonic disease?

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## ABSTRACT

**Background** The primary aim was to scrutinize our hypothesis: “Do more mature preterm (MMP) babies with surgical necrotizing enterocolitis (NEC) predominantly develop the colonic disease and are different in their response and behaviour in comparison to exceedingly preterm (EP) babies?” Secondary outcomes were to define time taken in developing NEC, time from diagnosis to laparotomy, requirement of parenteral nutrition (PN), and ventilatory support.

**Methods** We defined MMP babies as  $\geq 30$  weeks of gestation and EP babies as  $\leq 29$  weeks<sup>+6 days</sup> of gestation. Inclusion criteria were all babies  $< 37$  weeks with NEC requiring surgery (called surgical NEC group). Data were collected retrospectively and analyzed using QuickCalcs.

**Results** Of the total, 41% (97/234) of babies underwent laparotomy between 2010 and 2019. Totally, 81% were EP and 19% were MMP babies. Pure colonic involvement was seen in 9% of EP babies in comparison to 56% in the MMP babies ( $p=0.0001$ ). Involvement of only the small bowel was seen in two-thirds of EP babies in comparison to only one-third in MMP babies ( $p=0.01$ ). EP cohort required PN for 82 days (median) in comparison to 17 days (median) in the MMP cohort ( $p=0.001$ ). Ventilation requirement in the EP group versus the MMP group was 24 vs 9 days (median), respectively ( $p=0.0006$ ).

**Conclusions** MMP babies predominantly developed colonic disease, whereas EP babies predominantly developed small bowel disease. EP babies required a longer duration of PN and ventilation support. This study opens a new area of research to differentiate pathogenesis and maturation patterns of the small and large bowels in babies with NEC.

## INTRODUCTION

The incidence of necrotizing enterocolitis (NEC) is 1%–5% of those neonates hospitalized in intensive care units, of whom 90%–95% are premature. The mortality rate for preterm infants has not changed significantly in the past two decades. The incidence, severity, and mortality increase with increasing prematurity. The mortality in extremely low birth weight ( $< 1000$  g) is 30%–50%, and it is 10%–30% in

## Key messages

### What is already known about this subject?

- ▶ Necrotizing enterocolitis (NEC) is the leading cause of morbidity in preterm infants, affecting nearly 10% of preterm infants with a birth weight of  $< 1500$  g.
- ▶ The aetiopathogenesis of NEC is related to the maturity of the gastrointestinal tract.
- ▶ The incidence, severity, morbidity, and mortality increase with increasing prematurity.

### What are the new findings?

- ▶ In surgical NEC babies, the more mature preterm (MMP) babies predominantly developed colonic NEC, whereas the exceedingly preterm (EP) babies had more tendency to develop small bowel NEC.
- ▶ Babies with less than 1000 g were more likely to develop pure small bowel NEC than babies with a birth weight of more than 1000 g.
- ▶ In comparison with the MMP babies, the EP babies required a longer duration of parenteral nutrition and ventilation support.

### How might it impact on clinical practice in the foreseeable future?

- ▶ This study opens a new area of research to differentiate pathogenesis and maturation patterns of the small and large bowel in babies with NEC, which could have an impact on the surgical management of these babies.

infants with very low birth weight ( $< 1500$  g).<sup>1</sup> Mortality goes up to 40%–50% when surgery is required.<sup>2,3</sup> NEC is also the leading cause of morbidity in preterm infants, affecting nearly 10% of preterm infants with a birth weight of  $< 1500$  g.<sup>4</sup> This study was set with the primary aim to scrutinize the hypothesis “Do more mature preterm (MMP) babies (ie,  $\geq 30$  weeks of gestation) with surgical NEC predominantly develop the colonic disease?”. The secondary outcomes were to assess the difference in their behavior and outcomes, such as time taken in developing NEC after birth, time from diagnosis to laparotomy, the requirement of parenteral nutrition



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(PN), ventilatory support, and the death rate. The evidence around this hypothesis also was explored in the literature to find out the clinical importance of the outcomes.

## METHODS

We defined MMP babies as  $\geq 30$  weeks of gestation and exceedingly preterm (EP) babies as  $\leq 29$  weeks<sup>+6 days</sup> of gestation. Inclusion criteria were all babies  $< 37$  weeks with confirmed NEC and requiring surgery (surgical NEC). The diagnosis of NEC was made based on standard clinical and radiological criteria. Bell stage II and above were used as a definition. Clinical criteria were clinical unwellness, abdominal tenderness, bleeding per rectal, and abdominal discoloration. Radiological criteria were pneumatosis, portal venous gas, fixed bowel loops, and signs of perforation.

The exclusion criteria were preterm infants with NEC who had not required surgery and spontaneous intestinal perforation. After local approval, data were collected retrospectively from our databases (Badger Net and Surgical handover database) for the last 10 years using code for “necrotizing enterocolitis” or suspected necrotizing enterocolitis. Data were then cleaned using the clinical and the radiological criterion. The final cohort was diagnosed based on the aforementioned criteria by a single senior person (AK) supervising other three persons (IA, SM, and SB). Data were analyzed using QuickCalcs (GraphPad, La Jolla, California, USA). Fisher’s exact test was used for categorical data and the t-test was used for continuous data with a p value below 0.05 considered as significant.

## RESULTS

A total of 97 babies with a diagnosis of surgical NEC underwent laparotomy during the 10-year period

(January 2010–December 2019), which constituted 41% (97/234) of the total babies with NEC.

## Outcomes of EP and MMP

Of the total 97 babies with surgical NEC, 81% (79/97) were EP babies, whereas the rest of the 19% (18/97) were MMP babies. Pure colonic involvement was seen in only 9% (7/79) of the EP babies in comparison to 56% (10/18) in the MMP babies, and this difference was highly significant ( $p=0.0001$ ). Similarly, the involvement of only small bowel was seen in two-thirds (52/79) of EP babies in comparison to only one-third (6/18) of MMP babies, which was also significant ( $p=0.01$ ). The median gestation of the EP group was 25 weeks in comparison with the MMP group, whose median gestation age was 31 weeks. Another significant finding was the requirement of PN. EP cohort required PN for a median duration of 82 days in comparison to 17 days in the MMP cohort, and this difference was significant ( $p=0.001$ ). Similarly, the duration of the requirement of ventilation was significantly higher ( $p=0.0006$ ) in the EP group in comparison with the MMP group, which was 24 days (median) and 9 days (median), respectively. The babies with birth weight of  $< 1000$  g were more likely to have pure small bowel disease [odd ratio (OR) 2.9, 95% confidence interval (CI) 1.6 to 10.4,  $p=0.0028$ ]. Further details are shown in [table 1](#).

## Other outcomes

The median gestation of babies with NEC who needed surgery was 28 weeks<sup>+5 days</sup> (range 22 weeks<sup>+5 days</sup>–36 weeks<sup>+1 day</sup>) and median weight was 780 g (range 399–1960 g). Totally, 53% (52/97) of the babies were male and 70% (68/97) of babies received at least one complete course

**Table 1** Comparative outcomes of patients between EP and MMP group

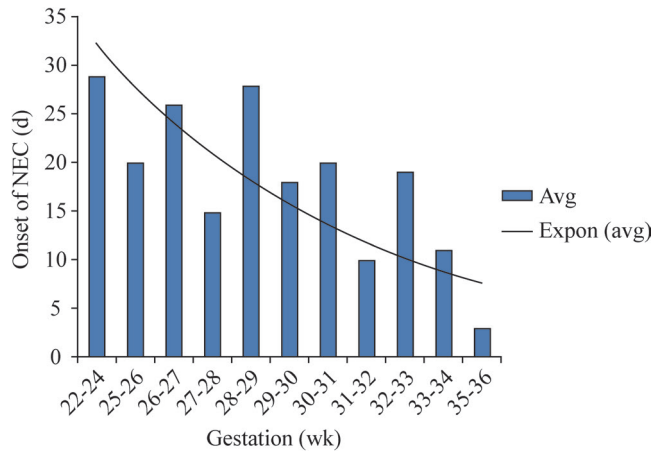
	EP	MMP	P value
Total number, n (%)	79 (81)	18 (19)	
Pure colonic involvement, n (%)	7 (9)	10 (56)	<b>0.0001</b>
Pure small bowel involvement, n (%)	52 (66)	6 (33)	<b>0.01</b>
Gestation (wk+d), median (range)	25 (22.7–<29+6)	31 ( $\geq 30$ –36+5)	<b>0.01</b>
Antenatal steroid used, n (%)*	66 (84)	15 (83)	1.00
	Incomplete course in 9	Incomplete course in 4	
Disease onset (d), median (range)	17 (2–79)	14 (3–46)	0.21
Time to laparotomy from onset of NEC (d), median (range)	4 (0–57)	3 (0–35)	0.96
Duration of parenteral nutrition required (d), median (range)	82 (10–196)	17 (7–108)	<b>0.001</b>
Duration of ventilation (d), median (range)	24 (3–129)	9 (2–17)	<b>0.0006</b>
Duration of inotropes required (d), median (range)†	1 (0–36)	0 (0–5)	0.39
	Only 47 required inotropes	Only seven required inotropes	
Death, n (%)	20 (25)	3 (17)	0.54

Values in bold indicates statistically significant.

\*Nine patients used antenatal steroid with incomplete course in EP group, while 4 patients in MMP group.

†Forty-four patients required inotropes in EP groups, while only seven patients in MMP group.

EP, exceedingly preterm; MMP, more matured preterm; NEC, necrotizing enterocolitis.



**Figure 1** Showing the day of the onset of NEC in relation to the gestation. Avg, average; NEC, necrotizing enterocolitis.

of antenatal steroids. Only 20% (20/97) of babies were born at our center. The rest 80% (77/97) were referred from other centers. Only one-third (33/97) of babies with NEC were fully established on enteral feeds before developing NEC. The median age of onset of illness was the end of the second week of life. We observed that increasing gestation was associated with earlier onset of disease (figure 1).

Approximately one-third (33/97) of babies with NEC had positive blood culture. None of these babies had cardiogenic NEC. Of total 97 babies, 60% (n=58) had pure small bowel disease; 17% (n=17) had pure colonic disease, with the rest of the 23% (n=22) having mixed small and large bowel diseases. The mean gestational age for babies with pure small bowel disease was 26 weeks<sup>+1 day</sup>, whereas it was 29 weeks<sup>+2 days</sup> for babies with pure colonic disease. Babies with pure colonic disease were heavier than babies with pure small bowel disease or mixed disease. Babies with pure colonic disease developed NEC slightly earlier than babies with pure small bowel disease (17 days vs 23 days), and this difference was statistically not significant. Table 2 demonstrates further characteristics based on disease location.

All-cause mortality for babies who underwent laparotomy for NEC was 23% (23/97). No significant difference was observed in the time taken from the onset of

disease to laparotomy in all three groups. No significant difference was observed in mortality and inotrope score in the three groups. Babies with pure small bowel NEC needed significantly (p=0.002) longer duration of PN than babies with pure colonic NEC (table 3).

## DISCUSSION

In the babies with NEC who underwent surgery, MMP babies had a significantly higher probability of developing colonic NEC in comparison to the EP babies. There is evidence in the literature that the aetiopathogenesis of NEC is related to the maturity of the gastrointestinal tract, bacterial colonization, and change in the micro-circulation.<sup>5 6</sup> These studies have also suggested that molecular factors might play an important role in distinguishing the mature bowel from the immature bowel. There is increasing evidence that the Toll-like receptor 4 (TLR4) is expressed at higher levels in the preterm than the full-term intestine of both humans and mice.<sup>7 8</sup> The colonization of the Gram-negative bacteria on the lining of the premature intestine causes activation of TLR4. This activation leads to increased release of proinflammatory cytokines, enhanced apoptosis of enterocytes, and impaired healing of the mucosal lining of the gut.<sup>9</sup> The Gram-negative bacterial translocation through the intestinal mucosa also leads to TLR4 activation on the lining of the bowel mesentery in the premature gut, which causes the development of ischemia and necrosis of the gut by reducing its blood supply and finally leading to NEC.<sup>10</sup> In utero, the elevated expression of TLR4 plays an important positive role in gut development via its effect on the “Notch signalling pathway”. Hence, if a baby is born prematurely, the TLR4 expression in the gut remains elevated.<sup>8</sup> So, the “in utero TLR4 signalling”, which was required for gut differentiation and development, becomes harmful for the premature gut after birth, predisposing it to NEC. This mechanism has also been named “the cross-switching hypothesis”.<sup>11</sup> This theory probably explains why premature babies are at increased risk of developing NEC and why NEC develops after bacterial colonization. However, this evidence also opens new areas of research, raising the question, “What is the

**Table 2** Patients’ characteristics based on disease location

	Small bowel (n=58)	Colonic (n=17)	Mixed (n=22)	Whole group
Gestation (wk+d), mean	26+3	29+2	27	28+5
Birth weight (g), mean	817	1181	837	780
Gender (male), n (%)	31 (53)	8 (47)	13 (59)	52 (53)
Antenatal steroids, n (%)	40 (69)	11 (64)	17 (77)	68 (70)
Inborn, n (%)	14 (24)	2 (11.7)	4 (18)	20 (20)
Feeds established prior to onset of disease, n (%)	30 (51)	11 (64)	8 (36)	33 (34)
Day of onset of disease	23	17	22	17
Positive blood culture, n (%)	20 (34)	6 (35)	7 (31)	33 (34)

**Table 3** Comparative outcomes of babies with pure small bowel and pure colonic NEC

	Small bowel (n=58)	Colonic (n=17)	P value
Time to laparotomy (d), median (range)	3 (1–40)	5 (0–35)	0.152
Mortality, n (%)	13 (22)	3 (17)	1.00
PN time for pre-NEC and post-NEC (d), median (range)	73 (10–148)	19 (7–83)	<b>0.002</b>
Inotrope time (d), median (range)	0.5 (0–3)	1 (0–5)	0.992

Values in bold indicates statistically significant.

NEC, necrotizing enterocolitis; PN, parenteral nutrition.

sequence of development of these changes in the gut? Does the small bowel mature before the large bowel? Why is the pattern of NEC different in more mature babies in comparison to less mature babies?”. Lastly, the most important question is “Are these EP babies different from MMP babies in terms of their aetiopathogenesis and the response to NEC, as their pattern of bowel involvement and postoperative requirements show definite differences?”.

There is some evidence in the literature that the term (>37 weeks of gestation) babies have a greater tendency for colon involvement in NEC,<sup>12–14</sup> but we cannot find any evidence that even the MMP (30–37 weeks of gestation) babies have a similar tendency. Our study opens a new area of research and discussion.

Our study also found that the EP cohort required PN for a significantly longer duration than the MMP cohort, which could be explained due to their significantly lower gestation and immaturity of the gut, as seen in immature infants and not likely to be a direct function of their NEC. Similarly, the duration of required ventilation was significantly higher in the EP group than the MMP group, which also highlights the immaturity of their lungs as well as the immune response in the EP group. The mortality was also higher (25% vs 17%) in the EP group, but statistically, this was not significantly different.

This study opens a new window of research in this field, raising questions about TLR4 activation, maturation of gut microbiota, and justification about primary anastomosis after small bowel NEC in MMP babies. As there is a higher tendency of colonic involvement in MMP babies, it probably indicates that the maturation (down-regulation) of TLR4 in the colon is developing at a rate different from that in the small gut, so small bowel down-regulation of TLR4 may take place earlier than that in the colon. Similarly, the maturation of microbiota, which is a protective mechanism, also probably travels from proximal to the distal gut. So, it will be interesting to know more about the microbiota of the small bowel and colon distinctly in MMP and EP babies, as the microbiota has an important impact on the severity and the outcomes of the disease. It will be also interesting to know when does the colon mature completely from NEC development of view. In our study, the median gestational age for MMP babies was 31 weeks. So, if the maturation of the colon completes around this age, probably primary anastomosis (after resection of the unhealthy bowel) will

be a safer and more widely acceptable operative option, which will avoid the complications of the stoma in these more matured preterm babies. Several studies have highlighted the benefits of primary anastomosis in babies with surgical NEC as an initial operative strategy in preterm babies.<sup>15 16</sup> As the pattern of involvement in the bowel is different in EP and MMP babies, probably this 30-week gestation can also play a role of a watershed gestation in future studies for NEC, but before committing to this gestational age, we need bigger multicenter studies.

Mortality in babies who underwent surgery has been reported as high as 50% in the literature.<sup>1 17</sup> Our overall mortality for surgical NEC was 23% (23/97). Looking individually at these two groups, the mortality in the EP group was slightly higher than that in the MMP group (25% vs 17%), but this difference was not statistically significant. This evidence indicates that the EP group needs higher support in terms of ventilation and nutrition, but mortality can be reduced with good support measures. The mortality in this study was in line with the other reported studies, and it has not changed much over the last two decades.<sup>1 17</sup>

Another noticeable observation was the relationship between the age (postbirth) of onset of NEC with the location of disease and gestation. Interestingly, the babies with pure colonic disease developed NEC slightly earlier than those with pure small bowel disease (17 days vs 23 days of life). The MMP cohort developed NEC slightly earlier than the EP cohort (14 days vs 17 days of life), but this difference was not statistically significant. There is evidence in the literature that NEC develops as early as 0–2 days of life in full-term infants.<sup>13</sup> The earliest onset of NEC in our MMP group was day 3 of life. Few other studies have found that the average onset of NEC in full-term infants is 4–9 days after birth, in comparison to 13 to 15 days in preterm babies.<sup>12 14 18</sup> The age of onset in our study is slightly later than these reported studies. We observed that increasing gestation was associated with earlier onset of disease. This observation has also been described by other authors.<sup>19</sup> The age of onset is also linked to the antibiotic policy. Early antibiotic exposure delays the maturation of the intestinal microbiome,<sup>19</sup> which can lead to the early onset of NEC. However, there is evidence in the literature that antibiotics have protective roles in developing NEC in preterm very low birthweight infants. It has been suggested that a better understanding is required about the role of variables



like time, type, and duration of antibiotic treatment on NEC incidence, immune development, gut colonization, and antibiotic resistance.<sup>20</sup> We follow our antibiotics policy strictly and start antibiotics only on strong clinical suspicion and laboratory investigation reports. This might explain the delay in the clinical presentation of our babies. However, another study has shown that the infants born at a median of 27 weeks of gestation would typically present with NEC at a median of 4–5 weeks of age and the infants born at closer to 37 weeks of gestation would develop NEC within the first 2 weeks of life.<sup>19</sup> Our babies developed NEC earlier than this series (figure 1). Regarding feeding, we have a milk bank and all preterm babies <32 weeks will routinely receive bank milk if the mother's expressed milk is not available. However, we also look after a lot of babies transferred to our unit "ex utero" from other centers. Hence, it is difficult to link feeding regimens with the disease onset, as milk bank is not available in all hospitals we receive babies from.

Of the total cohort, 60% (58/97) had pure small bowel disease, whereas 17% (17/97) had pure colon disease and 23% (22/97) showed mixed patterns (ie, both small and large bowel involvement). The median gestation and weight were higher in the babies with pure colonic disease in comparison with the babies with pure small bowel or mixed pattern involvement. This was a piece of indirect evidence that more matured babies with higher weight and gestation would have more tendency towards the involvement of the colon. Surgical intervention was required in 41% (97/237) of our patients, which was in keeping with the reported incidence of 20%–52% in these types of infants in the literature.<sup>21 22</sup>

One important limitation of this study was that only 41% of babies underwent surgery, so we were unable to comment on what were the pathologies in the larger cohorts of 59% non-operated babies with NEC. Another limitation was the small cohort of the patient especially in the MMP group (18/97), which might raise a possibility of type I statistical error, but the highly significant p value (p=0.0001) was an indicator of its minimization. This was a retrospective study using hospital episode statistics from the electronic databases, which might have the limitation of bias and confounding due to inaccuracies in data coding and incomplete data set. However, we have tried our best to correct those errors by correlating the data with our handover database and mortality–morbidity database.

In conclusion, in babies with surgical NEC, the MMP babies predominantly developed colonic NEC, whereas the EP babies had more tendency to develop small bowel NEC. Babies less than 1000 g were more likely to develop pure small bowel NEC than babies with a birth weight of more than 1000 g. In comparison to the MMP babies, the EP babies required a longer duration of PN and ventilation support. We strongly believe that this study will open the door to a new area of research to further understand and differentiate the responses, the pathogenesis, and the maturation patterns of the small bowel and the large

bowel with the special reference to NEC in EP and the MMP babies.

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