



# Outcomes for necrotising enterocolitis (NEC) in babies born at the threshold of viability: a case-control study

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**To cite:** Vallant N, Haffenden V, Peatman O, *et al.* Outcomes for necrotising enterocolitis (NEC) in babies born at the threshold of viability: a case-control study. *BMJ Paediatrics Open* 2022;**6**:e001583. doi:10.1136/bmjpo-2022-001583

Received 21 June 2022

Accepted 3 November 2022

## ABSTRACT

**Background** The threshold for active management of babies born prematurely in the UK is currently 22 weeks. The optimal management strategy for necrotising enterocolitis (NEC) in babies born at or near this threshold remains unclear.

**Aim** To review our institutional experience of babies born <24 weeks diagnosed with NEC, identify risk factors for NEC, and compare outcomes with a control cohort.

**Methods** All infants born <24 weeks gestation January 2015–December 2021 were identified. Babies diagnosed with NEC were defined as cases and babies with no NEC diagnosis as controls. Patient demographics, clinical features, complications and outcomes were extracted from the medical record and compared between cases and controls.

**Results** Of 56 babies, 31 (55.3%) were treated for NEC. There was no difference in NEC-specific risk factors between cases and controls. 17 babies (30.4%) underwent surgery, of these, 11/17 (64.7%) presented with a C reactive protein rise and 11/17 (64.7%) a fall in platelet count. Pneumatosis intestinalis (3/17 (17.7%)) or pneumoperitoneum (3/17 (17.7%)) were present in only a minority of cases. Abdominal ultrasound demonstrated intestinal perforation in 8/8 cases. The surgical complication rate was 5/17 (29.4%). There was no difference in the incidence of intraventricular haemorrhage, periventricular leukomalacia and survival to discharge between the groups.

**Conclusions** The diagnosis of NEC in infants born <24 weeks gestation is challenging with inconsistent clinical and radiological features. Ultrasound scanning is a useful imaging modality. Mortality was comparable regardless of a diagnosis of NEC. Low gestational age is not a contraindication to surgical intervention in NEC.

## INTRODUCTION

Necrotising enterocolitis (NEC) is a potentially devastating condition, especially when surgical treatment becomes necessary. The true incidence of NEC is difficult to discern with variabilities in diagnostic criteria and data collection posing significant challenges. The most consistent finding in published reports of NEC is that the incidence has been relatively stable over time in very low birth weight (VLBW) infants (<1500 g at birth).

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Necrotising enterocolitis (NEC) is a potentially devastating condition, affecting approximately 10% of prematurely born neonates. The main risk factor for development of NEC is prematurity. The threshold for active treatment of preterm neonates is currently considered to be 22 weeks gestational age and there is currently not much data on surgical outcomes for this cohort.

## WHAT THIS STUDY ADDS

⇒ This study adds valuable information on surgical outcomes in babies born under 24 weeks of gestational age suffering from NEC. It highlights the importance of the use of ultrasound as an additional diagnostic tool when the diagnosis is unclear and it shows that surgery in this small cohort of patients had no major impact on outcomes in regards to survival to discharge, intraventricular haemorrhage or periventricular leukomalacia. Surgery should therefore be offered, when indicated, for this most vulnerable cohort.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study shows that babies in this cohort can have a good outcome with a 48.4% survival to discharge in those requiring surgery. In line with the British Association of Perinatal Medicine statement, we are likely to see more extremely premature infants under 24 weeks gestation in the future. This study will enable clinicians to discuss the prognosis with parents and the wider team. We also feel that our results might affect clinical practice by giving clinicians data an awareness of the impact of NEC on outcomes, and may reassure them that surgery is a reasonable intervention.



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Stoll<sup>1</sup> reported an incidence of 10% for NEC within this cohort in 1994, which is still commonly cited.<sup>2–5</sup> This incidence of 10% has also been reported in the PIPS trial in 2016; a multicentre UK trial investigating the effect of probiotics on the development of NEC and late-onset sepsis.<sup>6</sup> The incidence of 'surgical' NEC is easier to determine, however, and

has not changed significantly over the past decade, still affecting 1–3 per 1000 live births and 1%–5% of infants admitted to Neonatal intensive care units (NICUs).<sup>1</sup>

In the UK, the improved survival of babies born at 22 weeks of gestation led the British Association of Perinatal Medicine (BAPM) to update their guidelines regarding perinatal management of these babies. They recommend that decisions should not be based on gestational age alone but should reflect ‘assessment of the baby’s prognosis taking into account multiple factors and follow multiprofessional discussions with parents.’<sup>7</sup>

The primary risk factor for the development of NEC is prematurity.<sup>8</sup> Well-accepted secondary risk factors are intrauterine growth retardation, the presence of pathogenic organisms in the gastrointestinal tract, bowel ischaemia, enteral feeding and variations in clinical practice regarding feeding (eg, breast milk vs donor breast milk or formula) and antibiotic treatment protocols.<sup>9</sup> The administration of antenatal maternal magnesium sulphate ( $\text{MgSO}_4$ ), intended as a neuroprotective measure, has been suggested to be an additional risk factor for the development of NEC.<sup>10–11</sup> In established NEC, clinical deterioration despite maximal medical therapy or the presence of pneumoperitoneum on abdominal X-ray represents the most common indications for surgical treatment, however, robust studies linking outcomes with specific indications for surgical interventions are lacking.<sup>12</sup>

The mortality rate of VLBW infants with surgical NEC is between 50% and 72%, and neurodevelopmental impairment is highly likely to occur in survivors.<sup>13–14</sup> Nevertheless, boundaries continue to be reset in regards to the minimal gestational age of babies at which active treatment should be considered, and with this, survival outcomes remain a focus of interest. Contemporary reports from European centres report survival rates of live-born extremely premature neonates to have improved significantly over the last two decades.<sup>15</sup> In live-born infants of 22 or 23 weeks gestational age, survival has been reported to reach almost 50% where active care is offered.<sup>16</sup> Similar outcomes were observed in a single centre study in Iowa, with a reported survival to hospital discharge of 78% among NICU admissions at 22 or 23 weeks gestational age.<sup>17</sup> The BAPM report that, despite being born alive and receiving active stabilisation, around 7 out of 10 babies (51%–79%) within the 22 week cohort die, and 6 out of 10 babies (56%–68%) within the 23-week cohort die.<sup>7</sup> Given the fragility and high mortality of babies born under 24 weeks gestation, the appropriateness of undertaking surgical intervention in this cohort for NEC or other abdominal emergency remains unclear. Anecdotally, many neonatal surgeons would not offer surgery for a baby under 24 weeks gestation on the grounds of futility. Others, however, would be prepared to attempt a laparotomy in these babies.

We aimed to further clarify the impact of NEC and the role of surgery in its management in babies born extremely prematurely by reviewing our institutional

experience of babies born under 24 weeks of completed gestational age. We set out to identify any potential risk factors for the development of NEC specifically in these babies. We compared the outcomes of babies diagnosed with NEC to a control group of equal gestational age but without a diagnosis of NEC. Furthermore, we compared the outcomes of babies undergoing surgery for NEC with those receiving only medical management for NEC and the control group without NEC to help define the role of surgery.

## METHODS

All infants admitted to our institution’s neonatal unit born <24 weeks gestation (22+0–23+6) between January 2015 and December 2021 were identified through the electronic medical record (BadgerNet, Clevermed). Gestational age was calculated from the mother’s first dating scan. Babies born both in our institution or in referring units, and subsequently transferred to our institution, were included. Subjects were divided into two groups: cases, where a diagnosis of NEC was made and controls, where no diagnosis of NEC was made, to examine potential risk factors for NEC. Cases of NEC were defined as those with a documented diagnosis of NEC on their clinical record and treated as such with either a minimum of 5 days of intravenous antibiotics in combination with gut rest or surgical intervention. During the period of our study, pneumoperitoneum was considered an absolute indication for surgical intervention and failure to improve clinically despite maximal medical treatment a relative indication. Those who underwent surgery were only included as cases where NEC was confirmed histologically in a resection specimen. Controls were babies born <24 weeks gestational age, who throughout their admission did not receive a diagnosis of NEC. Matching of cases and controls was not undertaken due to the likely small number of babies included and the risk of matching for a potentially significant factor.

## Exclusion criteria

Babies who died within 24 hours of birth and babies who underwent a laparotomy for suspected NEC but were found to have an alternative diagnosis were excluded.

## Data collection

Patient demographics, clinical features at the time of diagnosis of NEC, biochemical and radiological findings, surgical details, complications and survival data were extracted from the electronic medical record (BadgerNet). Commonly recognised potential risk factors for NEC were recorded including the use of ibuprofen for patent ductus arteriosus closure, the use of blood products, maternal chorioamnionitis, prolonged rupture of membranes, use of umbilical catheters and type of enteral feed given. Data on maternal age, smoking status, use of antenatal  $\text{MgSO}_4$  as well as steroids were obtained from maternal medical records. Outcome measures included

the grade of intraventricular haemorrhage (IVH) identified on routine cranial ultrasound screening, development of periventricular leukomalacia (PVL) and survival to discharge.

### Statistical analysis

For normally distributed data an independent samples t-test was used to compare means. For non-normally distributed data, a Kruskal-Wallis test was used to compare medians. Fisher's exact test with Bonferroni correction was used to compare categorical variables. IBM SPSS Statistics V.17 was used for all statistical analysis. A  $p < 0.05$  was considered statistically significant.

### Patient and public involvement

Patients and the public were not involved in conducting this research.

## RESULTS

### Patient demographics

Sixty-six babies were born <24 weeks during the 6-year study period. Six were excluded as they died within 24 hours of birth. Despite initial resuscitation for these babies, they failed to respond to intensive care treatment and their care was redirected. A further four babies who underwent a laparotomy but were not found to have NEC were excluded (three babies were found to have intussusception and one baby had peritoneal extravasation of parenteral nutrition). This left a cohort of 56 babies included in the study. Of 56 babies, 31 (55.4%) developed NEC during their admission (cases) while 25 (44.6%) did not and served as controls. The median gestational age was 23 weeks in both groups with seven babies (two controls and five cases) born at 22 weeks gestation. There was no statistically significant difference in weight or gender distribution although a notable preponderance of male infants was found in the cases as opposed to the reverse in the controls. [Table 1](#) summarises the key demographics of cases and controls.

### Antenatal and postnatal risk factors for NEC

[Table 2](#) summarises the potential antenatal and postnatal risk factors for NEC in cases and controls. Considering the small number of babies included and the large number of variables, no statistical analysis was attempted due to the high chance of a type 1 error. At our unit, trophic feeds up to a volume of 30 mL/kg/day expressed maternal breast milk, or donor-expressed breast milk

**Table 2** Antenatal data and potential postnatal risk factors for NEC

	Cases n=31	Controls n=25
Median maternal age (years)	33	31
MgSO <sub>4</sub> received (n (%))	19 (61.2)	20 (80)
Antenatal steroids received (n (%))	29 (93.5)	24 (96)
Maternal chorioamnionitis (n (%))	11 (35.5)	14 (56)
Prolonged rupture of membranes (n (%))	1 (3.2)	3 (12)
Maternal smoker (n (%))	3 (9.6)	2 (8)
Ibuprofen use for PDA closure (n (%))	6 (19.3)	4 (16)
Blood products given to baby (n (%))	31 (100)	25 (100)
Umbilical catheter use (n (%))	30 (96.8)	24 (96)
Maternal Breastmilk as first enteral feed (n (%))	25 (80.6)	24 (96)

NEC, necrotising enterocolitis; PDA, patent ductus arteriosus.

would have been given to every baby from the day of birth, assuming the abdomen remained soft and not distended, gastric aspirates were low volume, and there was no other contraindication.

### Outcomes

Cranial ultrasound findings and survival outcomes are summarised in [table 3](#).

IVH and PVL may be correlated with poor neurological outcomes but neurological or developmental testing was not performed as part of this study. Survival to discharge was similar in the two groups.

### Clinical features and outcomes of babies receiving only medical treatment for NEC (n=14)

The median age at the onset of suspected NEC was 12 days (3–83 days). Median C reactive protein (CRP) at the time of first clinical suspicion of NEC was 6.5 mg/L (<1–93 mg/L). 5 of 14 babies (35.7%) had a rise in their CRP from the previous day when first suspected to have NEC. Median platelet count was  $124 \times 10^9/L$  ( $33\text{--}517 \times 10^9/L$ ) with 5/14 (35.7%) patients experiencing a drop in the platelet count at the time of initial diagnosis.

**Table 1** Demographic data

	Cases (NEC) n=31	Controls n=25	P value
Median gestational age, range (weeks)	23 (22+5–23+6)	23 (22+6–23+6)	0.365
Mean±SD birth weight (g)	579±73	592±59	0.582
Gender (M:F)	18:13	9:16	0.116

NEC, necrotising enterocolitis.

**Table 3** Cranial ultrasound findings and survival data

	Cases n=31	Controls n=25	P value
Presence of any grade of IVH (%)	25 (80.6)	17 (68.0)	0.357
IVH grade (%)			0.282
Nil	6 (19.4)	8 (32)	
I	5 (16.1)	0 (0)	
II	6 (19.4)	6 (24)	
III	5 (16.1)	4 (16)	
IV	9 (29.0)	7 (28)	
PVL diagnosis (%)	6 (19.4)	2 (8.0)	0.277
Survival to discharge (%)	15 (48.4)	13 (52.0)	1.000

IVH, intraventricular haemorrhage; PVL, periventricular leukomalacia.

Survival to discharge was 7/14 (50%), the proportion of babies with PVL was 2/14 (14.2%), and the proportion with IVH 10/14 (71.4%).

#### Clinical features and outcomes of babies undergoing surgical treatment for NEC (n=17)

The median age at the onset of suspected NEC was 14 days (4–36 days). Median CRP at the time of first clinical suspicion of NEC was 23 mg/L (<1–250 mg/L). Eleven of 17 babies (64.7%) had a rise in their CRP from the previous day when first suspected to have NEC. Median platelet count was  $108 \times 10^9/L$  ( $13\text{--}289 \times 10^9/L$ ) with 11/18 (64.7%) patients experiencing a drop in the platelet count at the time of initial diagnosis.

On plain radiography, pneumatosis intestinalis was evident in 3/17 cases (17.7%), pneumoperitoneum in 3/17 (17.7%) and a paucity of intraluminal gas in 4/17 (23.5%). An abdominal USS was performed at the clinician's discretion in 8/17 (47.1%) cases where the diagnosis was unclear. In all eight cases, thickened, aperistalsic bowel with an extraluminal fluid collection, highly suspicious of an intestinal perforation, was identified.

Seventeen patients underwent laparotomy with a median time to surgery of 2 days<sup>1–5</sup> from the date of first suspicion of NEC. Findings at surgery were localised distal ileal disease with perforation in 9 (52.9%), multifocal NEC in 5 (29.4%), right iliac fossa inflammatory mass in 2 (11.8%) and extensive bowel necrosis in 2 (11.8%). A diverting ileostomy with a mucus fistula was fashioned in 13 (76.5%) and a high jejunostomy with a mucus fistula in 4 (23.5%).

Five out of 17 (29.4%) patients developed a postoperative wound dehiscence of which one went on to form an enterocutaneous fistula. One patient, after their initial laparotomy and ileostomy formation, developed a mass in the right iliac fossa and another perforation requiring a repeat laparotomy and bowel resection. Four weeks later, the patient developed further ileal perforations

requiring a third laparotomy, with formation of another ileostomy and mucus fistula. Four months after the initial operation, the patient had restoration of enteral continuity. There were no stoma-related complications or intra-abdominal abscess identified in our study cohort.

In this group of babies with surgically managed NEC, survival to discharge was 8/17 (47.1%). The proportion of babies with PVL was 4/17 (23.5%), and the proportion of babies with IVH 15/17 (88.2%).

#### DISCUSSION

We report our experiences and outcomes of babies born <24 weeks of gestational age over a period of 6 years, with special regard to the occurrence of NEC. Of 56 included babies, NEC was diagnosed in 31 (55.3%) of which 17 (30.4%) underwent surgery for NEC. We found no evidence of an increased risk of NEC associated with any of the risk factors examined. Survival to discharge in babies diagnosed with NEC was similar to babies with no NEC, at 48.4% vs 52.0%, regardless of the need for surgery. Development of NEC reduced survival by less than 10%, and surgery did not have an additional impact.

There was no statistically significant evidence of worse neurological injury in babies diagnosed with NEC. The overall number of babies with any degree of IVH was higher within the NEC cohort, however, a number of IVH grades III and IV were similar to the numbers in the control cohort. There was a trend towards a higher rate of PVL in babies diagnosed with NEC. However, in this study, it was not possible to correlate cranial ultrasound findings with neurodevelopmental outcomes. This will be the subject of a longer-term follow-up study.

The incidence of NEC in our study is higher than commonly described in studies reporting outcomes in extremely premature infants.<sup>1–6</sup> This is likely due to the fact that extreme prematurity and low birth weight are the two strongest risk factors for development of NEC. Our study includes only babies at the lowest end of gestational ages and weight, as opposed to previously published studies which generally include babies up to a gestational age of 28 weeks. The 2006 EPICURE2 Study reported survival of live born babies to be only 2% (n=3) for those born at 22 weeks' gestation, and 19% (n=66) at 23 weeks' gestation but when antenatal corticosteroids are given and babies are actively treated after birth, outcomes are much better.<sup>18</sup> Around the same time, survival rates of 30% for babies born at 22 weeks were reported from around the world, with similar neurodevelopmental outcomes as for babies born at 23 or 24 weeks.<sup>15–17 19</sup> This progress was backed up by the National Institute of Child Health and Human Development-funded Neonatal Research Network, reporting survival rates of 25% for babies born at 22 weeks.<sup>20</sup> Survival in our study was 52% in our control group of infants that did not develop NEC. This is higher than reported in the literature. However, the survival rate we report is skewed by the exclusion of patients that did not survive beyond 24

hours. Developing NEC and undergoing surgery did not appear to have a detrimental impact in terms of outcome when compared with our control cohort.

A protective effect of maternal breast milk on development of NEC has been described previously.<sup>21 22</sup> In our unit, we have a high exposure rate of premature babies to breast milk as their first enteral feed. There is uncertainty about the impact of antenatal MgSO<sub>4</sub> on the risk of developing NEC. Some studies have reported a positive association, especially in infants of very low gestational age<sup>10 11</sup> while others report a protective effect.<sup>23</sup> The findings in our cohort were of a higher proportion of controls (no diagnosis of NEC) receiving both MgSO<sub>4</sub> and maternal breast milk compared with cases. However, the numbers are insufficient to definitively claim a protective effect of either on the development of NEC and further, larger-scale, studies are still needed. In the meantime, we would continue to support the antenatal use of MgSO<sub>4</sub> and maternal breast milk as a first enteral feed.

We found that the clinical presentation of NEC in these extremely premature babies was atypical, but very much in concordance with the findings published by Battersby *et al*, that the clinical presentation of NEC can vary, dependent on gestational age.<sup>24</sup> With this, we acknowledge that without a reliable biomarker for NEC, identification of patients, especially in retrospect, is challenging, and for our study, poses a limitation. Of the 17 babies who underwent surgery for NEC, only around two-thirds showed a rise in CRP or a drop in platelets. Similarly, only a minority showed typical appearances on plain radiography with pneumatosis in 17.7% and pneumoperitoneum in 17.7%. We do not have a hypothesis for this lack in typical biochemical and radiological features, however, absence of a CRP rise could possibly be explained by an immature immune system being unable to mount a significant CRP response. Interestingly, where ultrasound scanning was deployed in unclear cases, features highly suspicious for intestinal perforation were identified in all cases. As a department, we have used ultrasound imaging as an adjunct to plain radiography and clinical assessment, when the diagnosis has been in doubt. Our radiologists are able to perform this at the cotside and have developed a wealth of experience in assessing the nature of the bowel, and looking specifically for collections and aperistalsic bowel, suggestive of a perforation. Conversely, at laparotomy, a very typical pattern of disease was found, with the majority located in the distal ileum and the remainder multifocal.

The rate of surgical complications was surprisingly low, with only 5 out of 17 babies (29.4%) developing wound dehiscences and no reported stomal complications other than one enterocutaneous fistula. It is not clear why this complication rate was so low given the fragility of the cohort. The patient who underwent multiple laparotomies appeared to have recurrent disease rather than complications of their initial surgery. Regarding neurological complications, we have only been able to assess findings on cranial ultrasound imaging as we only

followed patients to hospital discharge. More definitive neurodevelopmental outcomes as these babies grow into childhood will be of great interest.

The key strength of our study is the completeness of data collection and follow-up to the time of discharge, with a full data set for all infants included. However, the small sample size is the key limitation of our study. According to figures from the Office of National Statistics ([www.ons.gov.uk](http://www.ons.gov.uk)) for England and Wales, in 2018 the reported birth rates were 166 per annum for infants born at 22 weeks of gestation, and 313 per annum for infants born at 23 weeks of gestation, which in total is 479 babies each year. Given a population of roughly 10 million people in London, and our centre being one of 10 tertiary referral centres this equals a number of 47 babies <24 weeks we would expect to see in the course of 6 years. The 56 infants included are similar to this estimate. Nevertheless, it remains a small cohort, and therefore, the study is unlikely to be adequately powered to assess the impact of several potentially inter-related risk factors. It is also a retrospective study and so there may be unmeasured, confounding factors at play, including temporal trends. Given the rarity and heterogeneity of NEC in both its presentation and management, a large scale, prospective study looking at this cohort, in collaboration with the British Association for Perinatal Medicine (BAPM), would be of great interest. It would enable us to better define risk factors, diagnostic tools and optimal treatment strategies for NEC. Any such study must include long-term follow-up to determine the neurological outcomes for these infants.

In conclusion, the diagnosis of NEC in infants born <24 weeks gestation is more challenging than in babies born at a later gestational age. The clinical picture can be unclear with atypical radiological and highly variable haematological and biochemical findings. Early diagnosis of NEC in these infants will require a high index of suspicion and a heightened awareness of the differences in the presentation seen in this population. Ultrasound scanning may be a useful modality alongside more conventionally used radiological methods, especially where bowel perforation has occurred. Clinicians should have a low threshold for proceeding to ultrasound scanning in cases where there is any concern about an intra-abdominal event in a baby born under 24 weeks gestation. Although mortality remains high, survival in surgically managed patients can be similar to those developing NEC not requiring surgery or even in those not developing NEC at all. Therefore, surgery should be considered an integral part of intensive care for babies born at the threshold of viability.

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**Acknowledgements** We would like to acknowledge Dr. Salma Ayis, senior lecturer at King's College London, and thank her very much for her help with the statistical analyses for this study.

**Contributors** NV: manuscript preparation and revision, data collection; VH: statistical analysis, data collection; OP: data collection; HK: clinical supervision of project, revision of manuscript; GL: clinical supervision of project, revision of manuscript; HT: project supervision, preparation of manuscript, statistical analysis,



data collection; IY: conception of the study, project supervision, statistical analysis, manuscript revision and is guarantor for the study.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** The study was registered locally as a clinical service evaluation project (Number: 13449) and was not deemed to require further approval from an ethics committee as it involved anonymised, retrospective data collection only.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available on reasonable request.

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