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RISK FACTORS AND OUTCOMES FOR NECROTISING ENTEROCOLITIS (NEC) IN BABIES BORN AT THE THRESHOLD OF VIABILITY: A CASE-CONTROL STUDY

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ABSTRACT

Background: The threshold for active management of babies born prematurely in the UK is considered to be 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, identify risk factors for NEC and compare surgical outcomes with cases requiring medical treatment only, or not developing NEC.

Methods: All infants born <24 weeks gestation between January 2015-December 2021 were identified. Those undergoing surgery for NEC were designated as "cases", those with medically managed NEC "comparators" and those with no diagnosis of NEC "controls". Patient demographics, clinical features at the time of diagnosis, complications and outcomes were extracted from the electronic medical record and compared between groups.

Results: 31/56 (55.3%) babies were diagnosed with NEC. Multivariate analysis did not reveal any independent risk factors for NEC. 17 babies underwent surgery for NEC Their presentation was atypical with a CRP rise in only 11/17 (64.7%) and a fall in platelet count in 11/17 (64.7%). Pneumatosis intestinalis (3/17 (17.7%)) or pneumoperitoneum (3/17 (17.7%)) were only present in a minority of cases. Abdominal ultrasound demonstrated intestinal perforation in 8/8 cases. The surgical complication rate was 5/17 (29.4%). Survival to discharge in all three groups was 50%.

Conclusions:

The diagnosis of NEC in infants born <24 weeks gestation is challenging with inconsistent clinical and radiological features. Ultrasound scanning may be a useful modality. Low gestational age is not a contraindication to surgical intervention in NEC.

1. INTRODUCTION

Necrotising enterocolitis (NEC) is a potentially devastating condition, especially when surgical treatment becomes necessary. The incidence of surgical NEC has not changed significantly over the past decade, still affecting 1 to 3 per 1000 live births and 1% to 5% of infants admitted to NICUs (1). The true incidence of NEC is difficult to discern due to variabilities in current literature, with inconsistencies in diagnosis and data collection posing the biggest challenges. In particular the difficulties in confirming a diagnosis of NEC in mild cases (equivalent to Bells' Stage I) and differentiating from a diagnosis of spontaneous intestinal perforation (SIP) contribute to a lack of robust epidemiologic data (2,3).

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 (<1500g at birth). Stoll et al.(1) reported an incidence of 10% for NEC within this cohort in 1994, which is still commonly cited (4–7). This incidence of 10% has also been reported in the PiPS trial in 2016; a multicenter UK trial investigating the effect of probiotics on the development of NEC and late onset sepsis (8).

The primary risk factor for the development of NEC is prematurity (9). 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 and antibiotic treatment protocols (10). The administration of antenatal maternal magnesium sulphate ($MgSO_4$), intended as a neuroprotective measure, has been suggested to be an additional risk factor for the development of NEC (11,12). In established NEC, clinical deterioration despite maximal medical therapy, or the presence of pneumoperitoneum on abdominal x-ray represent the most common indications for surgical treatment, however, robust studies linking outcomes with specific indications for surgical interventions are lacking (13).

The mortality rate of VLBW infants with surgical NEC is between 50% and 72%, and neurodevelopmental impairment is highly likely to occur in survivors (14,15). Nevertheless, boundaries continue to be reset in regard to outcomes of babies with low gestational age. Contemporary reports from European centers report survival rates of live-born extremely premature neonates to have improved significantly over the last two decades (16). In live-born infants of 22 or 23 weeks gestational age, survival has been reported to reach almost 50% where active care is offered (17). Similar outcomes were observed in a single center study in Iowa, with a reported survival to hospital discharge of 78% amongst NICU admissions at 22 or 23 weeks gestational age (18).

In the UK the improved survival of babies born at 22 weeks of gestation led the British Association of Perinatal Medicine to update their guidelines regarding perinatal management of such babies. They recommend that decisions for such babies should not be based on gestational age alone but should reflect ‘assessment of the baby’s prognosis taking into account multiple factors’ and follow multi-professional discussions with parents (19). Although intensive care is now increasingly offered to

live born infants born between 22 and 24 weeks gestation, the role of surgical intervention in this cohort remains unclear.

We reviewed our institutional experience of babies born under 24 weeks completed gestational age in order to identify any potential risk factors for the development of NEC specifically in babies born under 24 completed weeks of gestation. Furthermore, we set out to compare the outcomes between babies requiring surgery for NEC, those requiring only medical treatment and a control group of babies with equal gestational age but without a diagnosis of NEC to help define the role of surgery.

2. METHODS

All infants admitted to our institution born <24 weeks gestation between January 2015 - December 2021 were identified through the electronic medical record (BadgerNet, Clevermed Ltd.). Any patient born outside our unit but transferred to us at a corrected gestation <24 weeks was also 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. A further sub-group analysis was then also performed to compare outcomes between medically treated, surgically treated and a control group of patients.

- **Cases:** babies diagnosed with NEC (proven on histology), undergoing surgery
- **Comparators:** babies diagnosed with NEC but managed conservatively
- **Controls:** babies that did not develop NEC during their hospital stay

2.1. Exclusion criteria

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

2.2. 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 included the use of ibuprofen for patent ductus arteriosus (PDA) closure, the use of blood products, maternal chorioamnionitis, prolonged rupture of membranes, use of umbilical catheters and the type of enteral feeds given. Data on maternal age, smoking status, use of antenatal $MgSO_4$ as well as steroids were obtained from maternal medical records. Outcome measures included the grade of intra-ventricular haemorrhage identified on routine cranial ultrasound screening, development of periventricular leukomalacia (PVL) and survival to discharge.

The study was registered locally as clinical service evaluation project (Number: 13449) and did not need approval by the ethics committee as it was a retrospective data collection only.

2.3. Statistical analysis

For normally distributed data an independent samples T-test was used to compare means between the groups. For non-normally distributed data a Kruskal-Wallis test was used to compare medians between the groups. Fisher's Exact test with Bonferroni

correction was used to compare categorical variables between groups. A binomial linear regression model was used to analyze potential risk factors for NEC. IBM SPSS Statistics v.17 was used for all statistical analysis. P<0.05 was considered statistically significant.

2.4. Patient and public involvement

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

3. RESULTS

3.1. Patient Demographics

Fifty-six babies <24 weeks were admitted during the 6-year study period. 31 out of 56 (55.3%) developed NEC during their admission, the other 25 cases served as controls. The median gestational age was 23 weeks in both groups and there was no difference in weight and gender distribution. The ratio of male to female in the NEC group was higher, however this was not statistically significant.

Table 1 below summarizes the key demographics across the 3 groups.

Table 1 – Demographic data of all babies <24 weeks included in the study

	Cases (NEC) ***n=31***	**Controls** ***n=25***	
Median gestational age (weeks)	23	23	0.365

Mean ± SD birthweight (g)	579 ± 73	592 ± 59	0.582
Gender (M:F)	18:13	9:16	0.116

3.2. Antenatal post-natal risk factors for NEC, univariate analysis

On univariate analysis, no statistically significant differences between groups were found for risk factors. There was a trend towards the first feed type (maternal breast milk) being protective, but this was not statistically significant. ***Table 2*** below summarizes these findings between the groups.

Table 2 – Antenatal data and potential post-natal risk factors for NEC

	Cases *n=31*	**Controls *n=25***	
Median maternal age (years)	33	31	p=0.666
Maternal smoker	3 (9.6%)	2 (8%)	p=0.827
$MgSO_4$ received (%)	19 (61.2%)	20 (80%)	p=0.130
Antenatal steroids received (%)	29 (93.5%)	24 (96%)	p=0.685
Ibuprofen use for PDA closure (%)	6 (19.3%)	4(16%)	p=0.745
Blood products (%)	31 (100%)	25 (100%)	-
Maternal chorioamnionitis (%)	11 (35.5%)	14 (56%)	p=0.125

Prolonged rupture of membranes (%)	1 (3.2%)	3 (12%)	p=0.205
Umbilical catheter use (%)	30 (96.8%)	24 (96%)	p=0.877
Maternal Breastmilk as first enteral feed (%)	25 (80.6%)	24 (96%)	p=0.084

3.3. Binomial logistic regression analysis

In order to further investigate the potential role of mentioned risk factors on development of NEC in our cohort a multivariate analysis was carried out. Antenatal and postnatal variables as described above with a p-value of <0.2 were entered into a binomial logistic regression analysis. None of the analysed risk factors were found to have a significant independent influence on the development of NEC.

Table 3 summarizes the results of the logistic regression analysis.

Table 3 – Binomial logistic regression analysis

Factor	OR	Lower 95% CI	Upper 95% CI	P-value
Antenatal $MgSO_4$	3.263	0.836	12.735	0.102
Chorioamnionitis	1.700	0.500	5.773	0.383
Maternal EBM first feed	0.211	0.020	2.202	0.138
Gender	0.398	0.119	1.336	0.103

3.4. Outcomes

Neuropathological and survival outcomes for all cases were obtained through electronic medical records. There was no difference in survival to discharge between the groups. There was a trend towards higher rates of intraventricular haemorrhage

(IVH) of any grade in babies undergoing surgical treatment for NEC (88.2%), when compared to babies being treated conservatively (71.4%) and controls (68.0%). Similarly, the diagnosis of periventricular leukomalacia (PVL), was observed more frequently in cases (23.5%) than in comparators (14.3%) or controls (8.0%). Neither reached statistical significance. ***Table 4*** summarizes these results.

Table 4 – Neurodevelopmental and survival data for all babies <24 weeks

	Cases ***n=17***	**Comparators** ***n=14***	**Controls** ***n=25***	
Presence of any grade of IVH (%)	15 (88.2%)	10 (71.4%)	17 (68.0%)	p=0.311
IVH grade (%)				p=0.604
Nil	2 (11.8%)	4 (28.6%)	8 (32.0%)	
I	3 (17.6%)	2 (14.3%)	0 (0.0%)	
II	4 (23.5%)	2 (14.3%)	6 (24.0%)	
III	3 (17.6%)	2 (14.3%)	4 (16.0%)	
IV	5 (29.4%)	4 (28.6%)	7 (28.0%)	
PVL diagnosis (%)	4 (23.5%)	2 (14.3%)	2 (8.0%)	p=0.369
Survival to discharge (%)	8 (47.1%)	7 (50.0%)	13 (52.0%)	p=0.952

3.5. Clinical features of babies undergoing surgical treatment for NEC (Cases, 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 23mg/L (<1-250mg/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 $108x10^9$/L ($13-289x10^9$/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 (17.7%), pneumoperitoneum in 3/17 (17.7%) and a paucity of intra-luminal gas in 4/17 (23.5%) cases. An abdominal USS was performed at the clinician's discretion in 8/17 (47.1%) cases where the diagnosis was unclear. In all 8 cases, thickened, aperistalsic bowel with an extra-luminal fluid collection, highly suspicious of an intestinal perforation, was identified.

These 17 patients underwent laparotomy with a median time to surgery of 2 days (1-5) from the date of first suspicion of NEC. Findings at surgery were: Distal ileal perforation in 9 (52.9%), multi-focal 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%).

5/17 (29.4%) patients developed a post-operative wound dehiscence of which one developed an enterocutaneous fistulae. One patient, after their initial laparotomy and ileostomy formation, developed a mass within the right iliac fossa and another perforation requiring a relaparotomy and bowel resection. 4 weeks later, the patient developed further ileal perforations requiring a 3rd laparotomy, with formation of another ileostomy and mucus fistula. 4 months after the initial operation, the patient had restoration of enteral continuity.

4. DISCUSSION

We report our experiences and outcomes of babies born <24 weeks of gestational age over a period of 6 years, with a special regard to the occurrence of NEC. To date, this is the largest reported series of neonates <24 weeks within the UK. Out of 56 included babies, NEC was diagnosed in 31 babies (55.3%) of which 17 (54.5%) underwent surgery for NEC. We found no evidence of an increased risk of NEC associated with any of the risk factors examined. Survival in babies diagnosed with NEC was the same as that in babies with no NEC, regardless of the need for surgery, at 50%. There was no statistically significant evidence of worse neurological injury in babies with NEC. but there was a trend towards increased risk of PVL with NEC, especially in those undergoing surgery for NEC.

The incidence of NEC in our study is higher than commonly described in the literature (1,4–8). It is likely that is due to previously published studies not looking at babies exclusively under 24 weeks gestation but have tended to also include extreme premature babies up to a gestation 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 (20). 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 (16–18,21). This

progress was backed up by the National Institute of Child Health and Human Development (NICHD)-funded Neonatal Research Network (NRN), reporting survival rates of 25% for babies born at 22 weeks (22). Survival in our study was better than any of these reports, even for those infants undergoing surgery, at 50%. This will have been skewed somewhat due our interest in NEC leading us to exclude infants not surviving at least 24 hours, but nevertheless, a 50% survival is very encouraging especially considering mortality of 50-72% previously reported for extremely low birth weight (ELBW) infants suffering from NEC (14,15).

A protective effect of maternal breast milk on development of NEC has been described before (23,24). In our unit, we have a high exposure rate of premature babies to breast milk as their first enteral feed. We found a higher rate of maternal breast milk administration in the control group than in the NEC cases (96.0% vs 80.6%) although this was not statistically significant on multivariate analysis. There is some controversy about the risk of NEC following antenatal $MgSO_4$ with some reports of an association, especially in infants of very low gestational age (11,12) whilst others report a protective effect [25]. We found $MgSO_4$ administration to be higher in the control group (80.0% vs. 61.2%), which whilst not definitive supports the possibility of a protective effect rather than an increased risk.

We found that the clinical presentation of the extremely premature babies with NEC was not typical. 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%. Interestingly, where ultrasound scanning was deployed

in unclear cases, features highly suspicious for intestinal perforation were identified in all cases. Conversely, at laparotomy a very typical pattern of disease was found, with the majority located in the distal ileum and the remainder multi-focal. The rate of surgical complications was surprisingly low, with just over a quarter developing wound dehiscence and no reported stomal complications other than one enterocutaneous fistula. The patient who underwent multiple laparotomies appeared to have recurrent disease rather than complications of their initial surgery. This compares very favourably to reported complication rate of up to 70% in extremely low birth weight neonates (25–28). Regarding neurological complications, we observed a trend towards higher proportions of PVL in the surgical cases. Our length of follow up was only to hospital discharge so neurodevelopmental outcomes are not yet available but will be of great interest.

The key strength of our study is the completeness of data collection and follow up, with a full data set for all infants included. Moreover, it is the largest UK-based study to date of infants born at this gestation. However, statistically, the size is the key limitation of our study. With only 56 infants included, we recognise the study may not be powered to assess the impact of several univariate 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, its presentation and its management, large scale prospective studies are needed to better define risk factors, diagnostic tools and optimal treatment strategies. These need to include long term follow up in order to determine the neurological outcomes for these infants.

In conclusion, the diagnosis of NEC in infants born <24 weeks gestation can be challenging. Ultrasound scanning may be a more useful modality than more conventionally used radiological methods. Although mortality remains high, survival in surgically managed patients can be the same as in 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 even for babies born at the threshold of viability.

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What is already known on this topic:

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 of viability for preterm neonates is currently considered to be 22 weeks gestational age and surgery 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 describes the largest cohort of such babies within the UK and gives extremely important insight into diagnostic- and treatment options.

How this study might affect clinical practice:

So far, not much was known on outcomes after surgery in this very vulnerable cohort of patients. Our study shows that babies under 24 weeks of gestational age undergoing surgery for NEC have similar outcomes to babies not suffering from NEC. Therefore this study might encourage clinicians around the world to offer active treatment, including surgery for NEC to these babies who are at the threshold of viability.

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RISK FACTORS AND OUTCOMES FOR NECROTISING ENTEROCOLITIS (NEC) IN BABIES BORN AT THE THRESHOLD OF VIABILITY: A CASE-CONTROL STUDY

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Necrotising Enterocolitis, Prematurity, Neonatology, Extreme Prematurity, Outcomes

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ABSTRACT

Background: The threshold for active management of babies born prematurely in the UK is considered to be 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 with a clinical diagnosis of NEC, identify risk factors for NEC, and compare outcomes with a control cohort.

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

Results: 31 out of 56 (55.3%) babies were treated for NEC, of those, 17 (54.9%) babies underwent surgery. There was no difference in NEC specific risk factors between the two groups. Babies who underwent surgery presented with a CRP rise in 11/17 (64.7%) and a fall in platelet count in 11/17 (64.7%). 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 incidence of IVH, PVL 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 may be a useful modality. Low gestational age is not a contraindication to surgical intervention in NEC.

1. INTRODUCTION

Necrotising enterocolitis (NEC) is a potentially devastating condition, especially when surgical treatment becomes necessary. The incidence of surgical NEC has not changed significantly over the past decade, still affecting 1 to 3 per 1000 live births and 1% to 5% of infants admitted to NICUs (1). The true incidence of NEC is difficult to discern due to variabilities in current literature, with inconsistencies in diagnosis and data collection posing the biggest challenges. In particular the difficulties in confirming a diagnosis of NEC in mild cases (equivalent to Bells' Stage I) and differentiating from a diagnosis of spontaneous intestinal perforation (SIP) contribute to a lack of robust epidemiologic data (2,3).

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 (<1500g at birth). Stoll et al.(1) reported an incidence of 10% for NEC within this cohort in 1994, which is still commonly cited (4–7). This incidence of 10% has also been reported in the PiPS trial in 2016; a multicenter UK trial investigating the effect of probiotics on the development of NEC and late onset sepsis (8).

The primary risk factor for the development of NEC is prematurity (9). 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 and antibiotic treatment protocols (10). The administration of antenatal maternal magnesium sulphate ($MgSO_4$), intended as a neuroprotective measure, has been suggested to be an additional risk factor for the

development of NEC (11,12). In established NEC, clinical deterioration despite maximal medical therapy, or the presence of pneumoperitoneum on abdominal x-ray represent the most common indications for surgical treatment, however, robust studies linking outcomes with specific indications for surgical interventions are lacking (13).

The mortality rate of VLBW infants with surgical NEC is between 50% and 72%, and neurodevelopmental impairment is highly likely to occur in survivors (14,15). Nevertheless, boundaries continue to be reset in regard to outcomes of babies with low gestational age. Contemporary reports from European centers report survival rates of live-born extremely premature neonates to have improved significantly over the last two decades (16). In live-born infants of 22 or 23 weeks gestational age, survival has been reported to reach almost 50% where active care is offered (17). Similar outcomes were observed in a single center study in Iowa, with a reported survival to hospital discharge of 78% amongst NICU admissions at 22 or 23 weeks gestational age (18).

In the UK the improved survival of babies born at 22 weeks of gestation led the British Association of Perinatal Medicine to update their guidelines regarding perinatal management of such babies. They recommend that decisions for such babies should not be based on gestational age alone but should reflect 'assessment of the baby's prognosis taking into account multiple factors' and follow multi-professional discussions with parents (19). Although intensive care is now increasingly offered to live born infants born between 22 and 24 weeks gestation, the role of surgical intervention in this cohort remains unclear.

We reviewed our institutional experience of babies born under 24 weeks completed gestational age in order to identify any potential risk factors for the development of NEC specifically in babies born under 24 completed weeks of gestation. Furthermore, we set out to compare the outcomes between babies requiring surgery for NEC, those requiring only medical treatment and a control group of babies with equal gestational age but without a diagnosis of NEC to help define the role of surgery.

2. METHODS

All infants admitted to our institution's neonatal unit born <24 weeks gestation between January 2015 - December 2021 were identified through the electronic medical record (BadgerNet, Clevermed Ltd.). Babies born both in our institution and in a referring unit 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 numbers of babies included and the risk of matching for a potentially significant factor.

2.1. 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 from the study.

2.2. 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 included the use of ibuprofen for patent ductus arteriosus (PDA) closure, the use of blood products, maternal chorioamnionitis, prolonged rupture of membranes, use of umbilical catheters and the type of enteral feeds given. Data on maternal age, smoking status, use of antenatal $MgSO_4$ as well as steroids were obtained from maternal medical records. Outcome measures included the grade of intra-ventricular haemorrhage identified on routine cranial ultrasound screening, development of periventricular leukomalacia (PVL) and survival to discharge.

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

2.3. Statistical analysis

For normally distributed data an independent samples T-test was used to compare means between the groups. For non-normally distributed data a Kruskal-Wallis test was used to compare medians between the groups. Fisher's Exact test with Bonferroni correction was used to compare categorical variables between groups. IBM SPSS Statistics v.17 was used for all statistical analysis. P<0.05 was considered statistically significant.

2.4. Patient and public involvement

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

3. RESULTS

3.1. Patient Demographics

Fifty-six babies born <24 weeks during the 6-year study period were included. 31 out of 56 (55.3%) developed NEC during their admission (cases), the other 25 served as controls. The median gestational age was 23 weeks in both groups and there was no statistically significant difference in weight or gender distribution although a preponderance of male infants was found in the cases. ***Table 1*** below summarizes the key demographics across the 3 groups.

Table 1 – Demographic data of all babies <24 weeks included in the study

	Cases (NEC) ***n=31***	**Controls** ***n=25***	
Median gestational age (weeks)	23	23	0.365

Mean ± SD birthweight (g)	579 ± 73	592 ± 59	0.582
Gender (M:F)	18:13	9:16	0.116

3.2. Antenatal- and post-natal risk factors for NEC

Table 2 summarizes the potential ante-natal and post-natal risk factors for NEC in cases and controls. Considering the small numbers of babies included and the large number of variables, no statistical analysis was attempted due to the high chance of a type 1 error. However, a higher incidence of antenatal $MgSO_4$ administration and use of maternal breast milk are observed in the control group.

Table 2 – Antenatal data and potential post-natal risk factors for NEC

	Cases	Controls
Median maternal age (years)	33	31
Maternal smoker (n (%))	3 (9.6%)	2 (8%)
$MgSO_4$ received (n (%))	19 (61.2%)	20 (80%)
Antenatal steroids received (n (%))	29 (93.5%)	24 (96%)
Ibuprofen use for PDA closure (n (%))	6 (19.3%)	4(16%)
Blood products (n (%))	31 (100%)	25 (100%)
Maternal chorioamnionitis (n (%))	11 (35.5%)	14 (56%)
Prolonged rupture of membranes (n (%))	1 (3.2%)	3 (12%)
Umbilical catheter use (n (%))	30 (96.8%)	24 (96%)
Maternal Breastmilk as first enteral feed (n (%))	25 (80.6%)	24 (96%)

3.3. Outcomes

Neuropathological and survival outcomes are summarized in ***Table 3.*** Although not statistically significant, a trend towards more severe neurological injury was observed in the cases compared to controls. Survival was equal in the two groups.

Table 3 – Neurodevelopmental and survival data for all babies <24 weeks

	Cases ***n=31***	**Controls** ***n=25***	
Presence of any grade of IVH (%)	25 (80.6%)	17 (68.0%)	p=0.357
IVH grade (%)			p=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%)	p=0.277
Survival to discharge (%)	15 (48.4%)	13 (52.0%)	p=1.000

3.4. Clinical features 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 23mg/L (<1-250mg/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 $108x10^9$/L ($13-289x10^9$/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 (17.7%), pneumoperitoneum in 3/17 (17.7%) and a paucity of intra-luminal gas in 4/17 (23.5%) cases. An abdominal USS was performed at the clinician's discretion in 8/17 (47.1%) cases where the diagnosis was unclear. In all 8 cases, thickened, aperistalsic bowel with an extra-luminal fluid collection, highly suspicious of an intestinal perforation, was identified.

These 17 patients underwent laparotomy with a median time to surgery of 2 days (1-5) from the date of first suspicion of NEC. Findings at surgery were: Localised distal ileal disease with perforation in 9 (52.9%), multi-focal 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%).

5/17 (29.4%) patients developed a post-operative wound dehiscence of which one developed an enterocutaneous fistulae. One patient, after their initial laparotomy and ileostomy formation, developed a mass within the right iliac fossa and another perforation requiring a relaparotomy and bowel resection. 4 weeks later, the patient developed further ileal perforations requiring a 3rd laparotomy, with formation of

another ileostomy and mucus fistula. 4 months after the initial operation, the patient had restoration of enteral continuity.

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 was 15/17 (88.2%).

4. DISCUSSION

We report our experiences and outcomes of babies born <24 weeks of gestational age over a period of 6 years, with a special regard to the occurrence of NEC. Out 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 in babies diagnosed with NEC was the same as that in babies with no NEC, regardless of the need for surgery, at around 50%. There was no statistically significant evidence of worse neurological injury but there was a trend towards a higher grade of IVH and the development of PVL in babies diagnosed with NEC.

The incidence of NEC in our study is higher than commonly described in studies reporting outcomes in extremely premature infants (1,4–8). It is likely that is due to previously published studies not looking at babies exclusively under 24 weeks gestation but have tended to also include babies up to a gestation 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 (20). 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 (16–18,21). This progress was backed up by the National Institute of Child Health and Human Development (NICHD)-funded Neonatal Research Network (NRN), reporting survival rates of 25% for babies born at 22 weeks (22). Survival in our study was better than any of these reports, even for those infants undergoing surgery, at 50%. This will have been skewed somewhat due our interest in NEC leading us to exclude infants not surviving at least 24 hours, but nevertheless, a 50% survival is very encouraging especially considering mortality of 50-72% previously reported for extremely low birth weight (ELBW) infants suffering from NEC (14,15).

A protective effect of maternal breast milk on development of NEC has been described before (23,24). In our unit, we have a high exposure rate of premature babies to breast milk as their first enteral feed. We found a higher rate of maternal breast milk administration in the control group than in the NEC cases (96.0% vs 80.6%). There is some uncertainty about the impact of antenatal $MgSO_4$ on the risk of developing NEC. Some studies have reported a positive association, especially in infants of very low gestational age (11,12) whilst others report a protective effect (25). We found $MgSO_4$ administration to be higher in the control group (80.0% vs. 61.2%).

We found that the clinical presentation of the extremely premature babies with NEC was not typical. 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%. Interestingly, where ultrasound scanning was deployed in unclear cases, features highly suspicious for intestinal perforation were identified in all cases. Conversely, at laparotomy a very typical pattern of disease was found, with the majority located in the distal ileum and the remainder multi-focal. The rate of surgical complications was surprisingly low, with just over a quarter developing wound dehiscence and no reported stomal complications other than one enterocutaneous fistula. The patient who underwent multiple laparotomies appeared to have recurrent disease rather than complications of their initial surgery. This compares very favorably to reported complication rate of up to 70% in extremely low birth weight neonates (26–29). Regarding neurological complications, we have only been able to analyze structural findings on imaging as our length of follow up was only 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, with a full data set for all infants included. However, the small sample size is the key limitation of our study. With only 56 infants included, we recognise the study may not be powered to assess the impact of several potentially interrelated 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, its presentation and its management, large scale prospective studies are needed to better define risk factors, diagnostic tools and optimal treatment strategies. These need to include long term follow up in order to determine the neurological outcomes for these infants.

In conclusion, the diagnosis of NEC in infants born <24 weeks gestation can be challenging. Ultrasound scanning may be a more useful modality than more conventionally used radiological methods. Although mortality remains high, survival in surgically managed patients can be the same as in 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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What is already known on this topic:

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 of viability for preterm neonates is currently considered to be 22 weeks gestational age and surgery 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 describes the largest cohort of such babies within the UK and gives extremely important insight into diagnostic- and treatment options.

How this study might affect clinical practice:

So far, not much was known on outcomes after surgery in this very vulnerable cohort of patients. Our study shows that babies under 24 weeks of gestational age undergoing surgery for NEC have similar outcomes to babies not suffering from NEC. Therefore this study might encourage clinicians around the world to offer active treatment, including surgery for NEC to these babies who are at the threshold of viability.

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risk factors and outcomes for Necrotising enterocolitis (NEC) in babies born at the threshold of viability: A case-control study

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OUTCOMES FOR NECROTISING ENTEROCOLITIS (NEC) IN BABIES BORN AT THE THRESHOLD OF VIABILITY: A CASE-CONTROL STUDY

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Necrotising Enterocolitis, Prematurity, Neonatology, Extreme Prematurity, Outcomes

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ABSTRACT

Background: The threshold for active management of babies born prematurely in the UK is considered to be 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 with a clinical diagnosis of NEC, identify risk factors for NEC, and compare outcomes with a control cohort.

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

Results: Of 56 babies, 31 (55.3%) were treated for NEC and 17/56 (30.4%) underwent surgery. There was no difference in NEC specific risk factors between the two groups. Babies who underwent surgery presented with a CRP rise in 11/17 (64.7%) and a fall in platelet count in 11/17 (64.7%). 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 incidence of IVH, PVL 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 may be a useful modality. Low gestational age is not a contraindication to surgical intervention in NEC.

1. INTRODUCTION

Necrotising enterocolitis (NEC) is a potentially devastating condition, especially when surgical treatment becomes necessary. The incidence of surgical NEC has not changed significantly over the past decade, still affecting 1 to 3 per 1000 live births and 1% to 5% of infants admitted to Neonatal intensive care units (NICUs) (1). The true incidence of NEC is difficult to discern. Variabilities in diagnostic criteria and data collection pose significant challenges.

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 such babies. They recommend that decisions for such babies should not be based on gestational age alone but should reflect 'assessment of the baby's prognosis taking into account multiple factors' and follow multi-professional discussions with parents (2).

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 (<1500g at birth). Stoll et al.(1) reported an incidence of 10% for NEC within this cohort in 1994, which is still commonly cited (3–6). This incidence of 10% has also been reported in the PiPS trial in 2016; a multicenter UK trial investigating the effect of probiotics on the development of NEC and late onset sepsis (7).

The primary risk factor for the development of NEC is prematurity (8). 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 (e.g. breast milk versus donor breast milk or formula), and antibiotic treatment protocols (9). The administration of antenatal maternal magnesium sulphate ($MgSO_4$), intended as a neuroprotective measure, has been suggested to be an additional risk factor for the development of NEC (10,11). In established NEC, clinical deterioration despite maximal medical therapy, or the presence of pneumoperitoneum on abdominal x-ray represent the most common indications for surgical treatment, however, robust studies linking outcomes with specific indications for surgical interventions are lacking (12).

The mortality rate of VLBW infants with surgical NEC is between 50% and 72%, and neurodevelopmental impairment is highly likely to occur in survivors (13,14). 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 centers report survival rates of live-born extremely premature neonates to have improved significantly over the last two decades (15). In live-born infants of 22 or 23 weeks gestational age, survival has been reported to reach almost 50% where active care is offered (16). Similar outcomes were observed in a single center study in Iowa, with a reported survival to hospital discharge of 78% amongst NICU admissions at 22 or 23 weeks gestational age (17). The British Association of Perinatal Medicine report that, despite being born alive and receiving active stabilization, a 3 out of 10 babies (51-79%) within the 22 week cohort, and 6 out of 10 babies (56-68%) within the 23 week cohort die (2). The role of surgical intervention in this cohort remains unclear.

We reviewed our institutional experience of babies born under 24 weeks completed gestational age in order to identify any potential risk factors for the development of

NEC specifically in babies born under 24 completed weeks of gestation. Furthermore, we set out to compare the outcomes between babies requiring surgery for NEC, those requiring only medical treatment and a control group of babies with equal gestational age but without a diagnosis of NEC to help define the role of surgery.

2. 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 Ltd.). Gestational age had been documented as per 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 numbers of babies included and the risk of matching for a potentially significant factor.

2.1. 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 (n=4, out of which 3 babies were found to have intussusception and one baby had suffered from TPN extravasation) excluded from the study.

2.2. 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 included the use of ibuprofen for patent ductus arteriosus (PDA) closure, the use of blood products, maternal chorioamnionitis, prolonged rupture of membranes, use of umbilical catheters and the type of enteral feeds given. Data on maternal age, smoking status, use of antenatal $MgSO_4$ as well as steroids were obtained from maternal medical records. Outcome measures included the grade of intra-ventricular haemorrhage identified on routine cranial ultrasound screening, development of periventricular leukomalacia (PVL) and survival to discharge.

The study was registered locally as 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.

2.3. Statistical analysis

For normally distributed data an independent samples T-test was used to compare means between the groups. For non-normally distributed data a Kruskal-Wallis test was used to compare medians between the groups. Fisher's Exact test with Bonferroni correction was used to compare categorical variables between groups. IBM SPSS Statistics v.17 was used for all statistical analysis. $P<0.05$ was considered statistically significant.

2.4. Patient and public involvement

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

3. RESULTS

3.1. Patient Demographics

Fifty-six babies born <24 weeks during the 6-year study period were included. Out of 56 (55.3%) babies, 31 developed NEC during their admission (cases), the other 25 served as controls. The median gestational age was 23 weeks in both groups and there was no statistically significant difference in weight or gender distribution although a preponderance of male infants was found in the cases. ***Table 1*** below summarises the key demographics across the 3 groups.

Table 1 – Demographic data of all babies <24 weeks included in the study

	Cases (NEC) ***n=31***	**Controls** ***n=25***	
Median gestational age (weeks)	23	23	0.365

Mean ± SD birthweight (g)	579 ± 73	592 ± 59	0.582
Gender (M:F)	18:13	9:16	0.116

3.2. Antenatal- and post-natal risk factors for NEC

Table 2 summarises the potential ante-natal and post-natal risk factors for NEC in cases and controls. Considering the small numbers 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 30ml/kg/day expressed maternal breast milk (EBM), or alternatively donor expressed breast milk (DEBM) would have been given to every baby from the day of birth, given the abdomen is soft, gastric aspirates are small volume, and there is no other contraindication.

Table 2 – Antenatal data and potential post-natal risk factors for NEC

	Cases	**Controls**
Median maternal age (years)	33	31
$MgSO_4$ 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%)

3.3. Outcomes

Neuropathological findings and survival outcomes are summarised in ***Table 3.***

Intra - ventricular hemorrhage (IVH) and Peri – ventricular leukomalacia (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.

Table 3 – Neuropathological and survival data for all babies <24 weeks

	Cases ***n=31***	**Controls** ***n=25***	
Presence of any grade of IVH (%)	25 (80.6%)	17 (68.0%)	p=0.357
IVH grade (%)			p=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%)	p=0.277
Survival to discharge (%)	15 (48.4%)	13 (52.0%)	p=1.000

3.4. Clinical features 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 23mg/L (<1-250mg/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 $108x10^9$/L ($13-289x10^9$/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 (17.7%), pneumoperitoneum in 3/17 (17.7%) and a paucity of intra-luminal gas in 4/17 (23.5%) cases. An abdominal USS was performed at the clinician's discretion in 8/17 (47.1%) cases where the diagnosis was unclear. In all 8 cases, thickened, aperistalsic bowel with an extra-luminal fluid collection, highly suspicious of an intestinal perforation, was identified.

These 17 patients underwent laparotomy with a median time to surgery of 2 days (1-5) from the date of first suspicion of NEC. Findings at surgery were: Localised distal ileal disease with perforation in 9 (52.9%), multi-focal 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%).

A number of 5 out of 17 (29.4%) patients developed a post-operative wound dehiscence of which one developed an enterocutaneous fistulae. One patient, after

their initial laparotomy and ileostomy formation, developed a mass within the right iliac fossa and another perforation requiring a relaparotomy and bowel resection. 4 weeks later, the patient developed further ileal perforations requiring a 3rd laparotomy, with formation of another ileostomy and mucus fistula. 4 months after the initial operation, the patient had restoration of enteral continuity.

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

4. DISCUSSION

We report our experiences and outcomes of babies born <24 weeks of gestational age over a period of 6 years, with a special regard to the occurrence of NEC. Out 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 as for babies with no NEC, at 48.4% compared to 52.0%, respectively, 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 numbers of babies with any degree of IVH was higher within the NEC cohort, however, the numbers of IVH 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, for this study, neuropathological findings were

not correlated with neurodevelopmental outcomes. This will be subject for 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 (1,3–7). It is likely that is due to previously published studies not looking at babies exclusively under 24 weeks gestation but have tended to also include babies up to a gestation 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 (18). 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 (15–17,19). This progress was backed up by the National Institute of Child Health and Human Development (NICHD)-funded Neonatal Research Network (NRN), reporting survival rates of 25% for babies born at 22 weeks (20). 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, we acknowledge is skewed by the exclusion of patients that did not survive beyond 24 hours as part of this study. Developing NEC and requiring surgery in this cohort did not have an additional impact in terms of outcome when comparing it to our control cohort.

A protective effect of maternal breast milk on development of NEC has been described before (21,22). In our unit, we have a high exposure rate of premature babies to breast milk as their first enteral feed. There is some uncertainty about the impact of antenatal

$MgSO_4$ on the risk of developing NEC. Some studies have reported a positive association, especially in infants of very low gestational age (10,11) whilst others report a protective effect (23). Whilst in our cohort, no differences were seen in regards to MgSO4 administration, or exposure to breast milk as first enteral feed in premature babies, we would continue to recommend maternal breast milk as a first enteral feed, where possible.

We found that the clinical presentation of the extremely premature babies with NEC was atypical, but very much in concordance to the findings published by Battersby et. al, that the clinical presentation of NEC can vary, dependent on gestational age (24). 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 radio-morphological features, however, the lack in CRP rise could be explained due to possible poor immunity and an inability 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 have been able to perform this at the bedside and have developed a wealth of experience in assessing the nature of the bowel, and looking specifically for collections and aperistaltic bowel, which would be 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 multi-focal.

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. 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 analyse structural findings on imaging as our length of follow up was only 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) for England and Wales, in 2018, the reported birth rates were 166 per annum for 22 weekers, and 313 per annum for 23 weekers, which in total is 479 babies. 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. With 56 infants included, we acknowledge that for this cohort, it is a higher number than what we would expect to be included over 6 years, but that it is still a small cohort, and therefore, the study may not be powered to assess the impact of several potentially interrelated 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, its presentation and its management, a large scale, prospective study, in collaboration with the British

Association for Perinatal Medicine (BAPM) looking at this cohort, would be of great interest, to better define risk factors, diagnostic tools and optimal treatment strategies. These need to include long term follow up in order to determine the neurological outcomes for these infants. Perspectives of ethicists, neonatologists and health economists would add further interest.

In conclusion, the diagnosis of NEC in infants born <24 weeks gestation can be challenging. Ultrasound scanning may be a more useful modality than more conventionally used radiological methods. Although mortality remains high, survival in surgically managed patients can be similar as in 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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What is already known on this topic:

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, IVH or PVL. and should therefore be offered, when indicated, also for this most vulnerable cohort.

How this study might affect clinical practice:

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 BAPM 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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OUTCOMES FOR NECROTISING ENTEROCOLITIS (NEC) IN BABIES BORN AT THE THRESHOLD OF VIABILITY: A CASE-CONTROL STUDY

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OUTCOMES FOR NECROTISING ENTEROCOLITIS (NEC) IN BABIES BORN AT THE THRESHOLD OF VIABILITY: A CASE-CONTROL STUDY

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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.

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Necrotising Enterocolitis, Prematurity, Neonatology, Extreme Prematurity, Outcomes

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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 with a clinical diagnosis of 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 diagnosis of NEC as controls. Patient demographics, clinical features, complications and outcomes were extracted from the medical record and compared between groups.

Results: Of 56 babies, 31 (55.3%) were treated for NEC and 17 (30.4%) underwent surgery. There was no difference in NEC specific risk factors between the two groups. Babies who underwent surgery presented with a CRP rise in 11/17 (64.7%) and a fall in platelet count in 11/17 (64.7%). 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 incidence of IVH, PVL 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 may be a useful modality. Mortality was similar in both groups. Low gestational age is not a contraindication to surgical intervention in NEC.

1. INTRODUCTION

Necrotising enterocolitis (NEC) is a potentially devastating condition, especially when surgical treatment becomes necessary. The incidence of surgical NEC has not changed significantly over the past decade, still affecting 1 to 3 per 1000 live births and 1% to 5% of infants admitted to Neonatal intensive care units (NICUs) (1). The true incidence of NEC is difficult to discern. Variabilities in diagnostic criteria and data collection pose significant challenges.

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 multi-professional discussions with parents (2).

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 (<1500g at birth). Stoll et al.(1) reported an incidence of 10% for NEC within this cohort in 1994, which is still commonly cited (3–6). This incidence of 10% has also been reported in the PiPS trial in 2016; a multicenter UK trial investigating the effect of probiotics on the development of NEC and late onset sepsis (7).

The primary risk factor for the development of NEC is prematurity (8). 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 (e.g. breast milk versus donor breast milk or formula), and antibiotic treatment protocols (9). The administration of antenatal maternal magnesium sulphate ($MgSO_4$), intended as a neuroprotective measure, has been suggested to be an additional risk factor for the development of NEC (10,11). In established NEC, clinical deterioration despite maximal medical therapy, or the presence of pneumoperitoneum on abdominal x-ray represent the most common indications for surgical treatment, however, robust studies linking outcomes with specific indications for surgical interventions are lacking (12).

The mortality rate of VLBW infants with surgical NEC is between 50% and 72%, and neurodevelopmental impairment is highly likely to occur in survivors (13,14). 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 centers report survival rates of live-born extremely premature neonates to have improved significantly over the last two decades (15). In live-born infants of 22 or 23 weeks gestational age, survival has been reported to reach almost 50% where active care is offered (16). Similar outcomes were observed in a single center study in Iowa, with a reported survival to hospital discharge of 78% amongst NICU admissions at 22 or 23 weeks gestational age (17). The British Association of Perinatal Medicine report that, despite being born alive and receiving active stabilization, a 3 out of 10 babies (51-79%) within the 22 week cohort, and 6 out of 10 babies (56-68%) within the 23 week cohort die (2). The role of surgical intervention in this cohort remains unclear.

We reviewed our institutional experience of babies born under 24 weeks completed gestational age in order to identify any potential risk factors for the development of NEC specifically in babies born under 24 completed weeks of gestation. Furthermore, we set out to compare the outcomes between babies requiring surgery for NEC, those requiring only medical treatment and a control group of babies with equal gestational age but without a diagnosis of NEC to help define the role of surgery.

2. 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 Ltd.). Gestational age had been documented as per 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 numbers of babies included and the risk of matching for a potentially significant factor.

2.1. 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.

2.2. 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 included the use of ibuprofen for patent ductus arteriosus (PDA) closure, the use of blood products, maternal chorioamnionitis, prolonged rupture of membranes, use of umbilical catheters and the type of enteral feeds given. Data on maternal age, smoking status, use of antenatal $MgSO_4$ as well as steroids were obtained from maternal medical records. Outcome measures included the grade of intra-ventricular haemorrhage identified on routine cranial ultrasound screening, development of periventricular leukomalacia (PVL) and survival to discharge.

The study was registered locally as 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.

2.3. Statistical analysis

For normally distributed data an independent samples T-test was used to compare means between the groups. For non-normally distributed data a Kruskal-Wallis test was used to compare medians between the groups. Fisher's Exact test with Bonferroni correction was used to compare categorical variables between groups. IBM SPSS Statistics v.17 was used for all statistical analysis. $P<0.05$ was considered statistically significant.

2.4. Patient and public involvement

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

3. RESULTS

3.1. Patient Demographics

66 babies were born <24 weeks during the 6-year study period. 6 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 re-directed. A further 4 babies who underwent a laparotomy but were not found to have NEC were excluded (3 babies were found to have intussusception and one baby had suffered from TPN extravasation). This left a cohort of 56 babies included in the study. Out of 56 babies, 31 (55.4%) developed NEC during their admission (cases) whilst 25 (44.6%) did not and served as controls. The median gestational age was 23 weeks in both groups and there was no statistically significant difference in weight or gender distribution although a preponderance of male infants was found in the cases. There were 7 babies in total born at 22 weeks gestation that were included in the study (2 controls and 5 cases).

Table 1 below summarises the key demographics across the 3 groups.

Table 1 – Demographic data of all babies <24 weeks included in the study

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

3.2. Antenatal- and post-natal risk factors for NEC

Table 2 summarises the potential ante-natal and post-natal risk factors for NEC in cases and controls. Considering the small numbers 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 30ml/kg/day expressed maternal breast milk (EBM), or alternatively donor expressed breast milk (DEBM) would have been given to every baby from the day of birth, assuming the abdomen remains soft and not distended, gastric aspirates are low volume, and there is no other contraindication.

Table 2 – Antenatal data and potential post-natal risk factors for NEC

	Cases ***n=31***	**Controls** ***n=25***
Median maternal age (years)	33	31
$MgSO_4$ 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%)

3.3. Outcomes

Neuropathological findings and survival outcomes are summarised in ***Table 3.***

Intra - ventricular hemorrhage (IVH) and Peri – ventricular leukomalacia (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.

Table 3 – Neuropathological and survival data for all babies <24 weeks

	Cases ***n=31***	**Controls** ***n=25***

Presence of any grade of IVH (%)	25 (80.6%)	17 (68.0%)	p=0.357
IVH grade (%)			p=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%)	p=0.277
Survival to discharge (%)	15 (48.4%)	13 (52.0%)	p=1.000

3.4. Clinical features 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 23mg/L (<1-250mg/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 $108x10^9$/L ($13-289x10^9$/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 (17.7%), pneumoperitoneum in 3/17 (17.7%) and a paucity of intra-luminal gas in 4/17 (23.5%) cases. An abdominal USS was performed at the clinician's discretion in 8/17 (47.1%) cases where the diagnosis was unclear. In all 8 cases, thickened, aperistalsic bowel

with an extra-luminal fluid collection, highly suspicious of an intestinal perforation, was identified.

These 17 patients underwent laparotomy with a median time to surgery of 2 days (1-5) from the date of first suspicion of NEC. Findings at surgery were: localised distal ileal disease with perforation in 9 (52.9%), multi-focal 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 post-operative wound dehiscence of which one developed an enterocutaneous fistulae. One patient, after their initial laparotomy and ileostomy formation, developed a mass within the right iliac fossa and another perforation requiring a relaparotomy 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 specific stoma-related complications or intra-abdominal abscess identified in our study.

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

4. DISCUSSION

We report our experiences and outcomes of babies born <24 weeks of gestational age over a period of 6 years, with a special regard to the occurrence of NEC. Out 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 numbers of babies with any degree of IVH was higher within the NEC cohort, however the numbers of IVH 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, for this study, neuropathological findings were not correlated 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 (1,3–7). This is likely due to the fact that extreme prematurity and low birth weight are the two strongest risk factors for development of NEC. This is one of the first studies exclusively analysing outcomes for babies at the low end of gestational ages and weight, as opposed to previously published studies which tended to 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 (18). 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 (15–17,19). This progress was backed up by the National Institute of Child Health and Human Development (NICHD)-funded Neonatal Research Network (NRN), reporting survival rates of 25% for babies born at 22 weeks (20). 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 reported is skewed by the exclusion of patients that did not survive beyond 24 hours as part of this study. Developing NEC and requiring surgery in this cohort did not have an additional impact in terms of outcome when comparing it to our control cohort.

A protective effect of maternal breast milk on development of NEC has been described before (21,22). In our unit, we have a high exposure rate of premature babies to breast milk as their first enteral feed. There is some uncertainty about the impact of antenatal $MgSO_4$ on the risk of developing NEC. Some studies have reported a positive association, especially in infants of very low gestational age (10,11) whilst others report a protective effect (23). Whilst in our cohort, no differences were seen in regards to MgSO4 administration, or exposure to breast milk as first enteral feed in premature babies, we would continue to recommend maternal breast milk as a first enteral feed, where possible.

We found that the clinical presentation of extremely premature babies with NEC 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 (24). 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 have been able to perform this at the bedside and have developed a wealth of experience in assessing the nature of the bowel, and looking specifically for collections and aperistalsic bowel, which would be 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 multi-focal.

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 analyse structural findings on imaging as our length of follow up was only 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) 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 six years. The 56 infants included, is 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 interrelated 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, its presentation and its management, a large scale, prospective study, in collaboration with the British Association for Perinatal Medicine (BAPM) looking at this cohort, would be of great interest, to better define risk factors, diagnostic tools and optimal treatment strategies. These need to include long term follow up in order to determine the neurological outcomes for these infants.

In conclusion, the diagnosis of NEC in infants born <24 weeks gestation can be challenging. Ultrasound scanning may be a useful modality in addition to more conventionally used radiological methods. 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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What is already known on this topic:

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, IVH, or PVL. Surgery should therefore be offered, when indicated, for this most vulnerable cohort.

How this study might affect clinical practice:

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 BAPM 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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OUTCOMES FOR NECROTISING ENTEROCOLITIS (NEC) IN BABIES BORN AT THE THRESHOLD OF VIABILITY: A CASE-CONTROL STUDY

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OUTCOMES FOR NECROTISING ENTEROCOLITIS (NEC) IN BABIES BORN AT THE THRESHOLD OF VIABILITY: A CASE-CONTROL STUDY

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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 CRP 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 incidence of IVH, PVL 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.

1. 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 (<1500g at birth). Stoll et al.(1) reported an incidence of 10% for NEC within this cohort in 1994, which is still commonly cited (2–5). This incidence of 10% has also been reported in the PiPS trial in 2016; a multicenter UK trial investigating the effect of probiotics on the development of NEC and late onset sepsis (6). The incidence of "surgical" NEC is easier to determine however, and has not changed significantly over the past decade, still affecting 1 to 3 per 1000 live births and 1% to 5% of infants admitted to Neonatal intensive care units (NICUs) (1).

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 multi-professional discussions with parents (7).

The primary risk factor for the development of NEC is prematurity (8). 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 (e.g. breast milk versus donor breast milk or formula), and antibiotic treatment protocols (9). The administration of antenatal maternal magnesium sulphate ($MgSO_4$), intended as a neuroprotective measure, has been suggested to be an additional risk factor for the development of NEC (10,11). In established NEC, clinical deterioration despite maximal medical therapy, or the presence of pneumoperitoneum on abdominal x-ray represent the most common indications for surgical treatment, however, robust studies linking outcomes with specific indications for surgical interventions are lacking (12).

The mortality rate of VLBW infants with surgical NEC is between 50% and 72%, and neurodevelopmental impairment is highly likely to occur in survivors (13,14). 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 centers report survival rates of live-born extremely premature neonates to have improved significantly over the last two decades (15). In live-born infants of 22 or 23 weeks gestational age, survival has been reported to reach almost 50% where active care is offered (16). Similar outcomes were observed in a single center study in Iowa, with a reported survival to hospital discharge of 78% amongst NICU admissions at 22 or 23 weeks gestational age (17). The British Association of Perinatal Medicine report that, despite being born alive and receiving active stabilization, 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 (7). 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 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.

2. 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 Ltd.). 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 numbers of babies included and the risk of matching for a potentially significant factor.

2.1. 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.

2.2. 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 (PDA) 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 $MgSO_4$ as well as steroids were obtained from maternal medical records. Outcome measures included the grade of intra-ventricular haemorrhage identified on routine cranial ultrasound screening, development of periventricular leukomalacia (PVL) and survival to discharge.

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.

2.3. 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. $P<0.05$ was considered statistically significant.

2.4. Patient and public involvement

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

3. RESULTS

3.1. Patient Demographics

66 babies were born <24 weeks during the 6-year study period. 6 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 re-directed. A further 4 babies who underwent a laparotomy but were not found to have NEC were excluded (3 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) whilst 25 (44.6%) did not and served as controls. The median gestational age was 23 weeks in both groups with 7 babies (2 controls and 5 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.

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 birthweight (g)	579 ± 73	592 ± 59	0.582
Gender (M:F)	18:13	9:16	0.116

3.2. Antenatal- and post-natal risk factors for NEC

Table 2 summarises the potential ante-natal and post-natal risk factors for NEC in cases and controls. Considering the small numbers 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 30ml/kg/day expressed maternal breast milk (EBM), or alternatively donor expressed breast milk (DEBM) 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.

Table 2 – Antenatal data and potential post-natal risk factors for NEC

	Cases ***n=31***	**Controls** ***n=25***
Median maternal age (years)	33	31
$MgSO_4$ 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%)

3.3. Outcomes

Cranial ultrasound findings and survival outcomes are summarised in Table 3. Intra-ventricular hemorrhage (IVH) and Peri-ventricular leukomalacia (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.

Table 3 – Cranial ultrasound findings and survival data

	Cases ***n=31***	**Controls** ***n=25***

Presence of any grade of IVH (%)	25 (80.6%)	17 (68.0%)	p=0.357
IVH grade (%)			p=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%)	p=0.277
Survival to discharge (%)	15 (48.4%)	13 (52.0%)	p=1.000

3.4. 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 CRP at the time of first clinical suspicion of NEC was 6.5mg/L (<1-93mg/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 $124x10^9$/L ($33-517x10^9$/L) with 5/14 (35.7%) patients experiencing a drop in the platelet count at the time of initial diagnosis. 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%).

3.5. 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 23mg/L (<1-250mg/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 $108x10^9$/L ($13-289x10^9$/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 intra-luminal 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 8 cases, thickened, aperistalsic bowel with an extra-luminal fluid collection, highly suspicious of an intestinal perforation, was identified.

Seventeen patients underwent laparotomy with a median time to surgery of 2 days (1-5) from the date of first suspicion of NEC. Findings at surgery were: localised distal ileal disease with perforation in 9 (52.9%), multi-focal 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 post-operative 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%).

4. DISCUSSION

We report our experiences and outcomes of babies born <24 weeks of gestational age over a period of 6 years, with a 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 numbers of babies with any degree of IVH was higher within the NEC cohort, however the numbers 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 (1–6). 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 (18). 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 (15–17,19). This progress was backed up by the National Institute of Child Health and Human Development (NICHD)-funded Neonatal Research Network (NRN), reporting survival rates of 25% for babies born at 22 weeks (20). 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 an detrimental impact in terms of outcome when compared to our control cohort.

A protective effect of maternal breast milk on development of NEC has been described previously (21,22). 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 $MgSO_4$ on the risk of developing NEC. Some studies have reported a positive association, especially in infants of very low gestational age (10,11) whilst others report a protective effect (23). The findings in our cohort were of a higher proportion of controls (no diagnosis of NEC) receiving both $MgSO_4$ and maternal breast milk compared to 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 $MgSO_4$ 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 (24). 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 multi-focal.

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) 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 six years. The 56 infants included, is 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 interrelated 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 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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What is already known on this topic:

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, IVH, or PVL. Surgery should therefore be offered, when indicated, for this most vulnerable cohort.

How this study might affect clinical practice:

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 BAPM 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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OUTCOMES FOR NECROTISING ENTEROCOLITIS (NEC) IN BABIES BORN AT THE THRESHOLD OF VIABILITY: A CASE-CONTROL STUDY

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OUTCOMES FOR NECROTISING ENTEROCOLITIS (NEC) IN BABIES BORN AT THE THRESHOLD OF VIABILITY: A CASE-CONTROL STUDY

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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.

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Necrotising Enterocolitis, Prematurity, Neonatology, Extreme Prematurity, Outcomes

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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 CRP 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 incidence of IVH, PVL 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.

1. 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 (<1500g at birth). Stoll et al.(1) reported an incidence of 10% for NEC within this cohort in 1994, which is still commonly cited (2–5). This incidence of 10% has also been reported in the PiPS trial in 2016; a multicenter UK trial investigating the effect of probiotics on the development of NEC and late onset sepsis (6). The incidence of "surgical" NEC is easier to determine however, and has not changed significantly over the past decade, still affecting 1 to 3 per 1000 live births and 1% to 5% of infants admitted to Neonatal intensive care units (NICUs) (1).

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 multi-professional discussions with parents (7).

The primary risk factor for the development of NEC is prematurity (8). 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 (e.g. breast milk versus donor breast milk or formula), and antibiotic treatment protocols (9). The administration of antenatal maternal magnesium sulphate ($MgSO_4$), intended as a neuroprotective measure, has been suggested to be an additional risk factor for the development of NEC (10,11). In established NEC, clinical deterioration despite maximal medical therapy, or the presence of pneumoperitoneum on abdominal x-ray represent the most common indications for surgical treatment, however, robust studies linking outcomes with specific indications for surgical interventions are lacking (12).

The mortality rate of VLBW infants with surgical NEC is between 50% and 72%, and neurodevelopmental impairment is highly likely to occur in survivors (13,14). 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 centers report survival rates of live-born extremely premature neonates to have improved significantly over the last two decades (15). In live-born infants of 22 or 23 weeks gestational age, survival has been reported to reach almost 50% where active care is offered (16). Similar outcomes were observed in a single center study in Iowa, with a reported survival to hospital discharge of 78% amongst NICU admissions at 22 or 23 weeks gestational age (17). The British Association of Perinatal Medicine report that, despite being born alive and receiving active stabilization, 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 (7). 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 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.

2. 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 Ltd.). 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 numbers of babies included and the risk of matching for a potentially significant factor.

2.1. 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.

2.2. 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 (PDA) 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 $MgSO_4$ as well as steroids were obtained from maternal medical records. Outcome measures included the grade of intra-ventricular haemorrhage identified on routine cranial ultrasound screening, development of periventricular leukomalacia (PVL) and survival to discharge.

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.

2.3. 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. $P<0.05$ was considered statistically significant.

2.4. Patient and public involvement

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

3. RESULTS

3.1. Patient Demographics

66 babies were born <24 weeks during the 6-year study period. 6 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 re-directed. A further 4 babies who underwent a laparotomy but were not found to have NEC were excluded (3 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) whilst 25 (44.6%) did not and served as controls. The median gestational age was 23 weeks in both groups with 7 babies (2 controls and 5 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.

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 birthweight (g)	579 ± 73	592 ± 59	0.582
Gender (M:F)	18:13	9:16	0.116

3.2. Antenatal- and post-natal risk factors for NEC

Table 2 summarises the potential ante-natal and post-natal risk factors for NEC in cases and controls. Considering the small numbers 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 30ml/kg/day expressed maternal breast milk (EBM), or alternatively donor expressed breast milk (DEBM) 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.

Table 2 – Antenatal data and potential post-natal risk factors for NEC

	Cases ***n=31***	**Controls** ***n=25***
Median maternal age (years)	33	31
$MgSO_4$ 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%)

3.3. Outcomes

Cranial ultrasound findings and survival outcomes are summarised in Table 3. Intra-ventricular hemorrhage (IVH) and Peri-ventricular leukomalacia (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.

Table 3 – Cranial ultrasound findings and survival data

	Cases ***n=31***	**Controls** ***n=25***

Presence of any grade of IVH (%)	25 (80.6%)	17 (68.0%)	p=0.357
IVH grade (%)			p=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%)	p=0.277
Survival to discharge (%)	15 (48.4%)	13 (52.0%)	p=1.000

3.4. 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 CRP at the time of first clinical suspicion of NEC was 6.5mg/L (<1-93mg/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 $124x10^9$/L ($33-517x10^9$/L) with 5/14 (35.7%) patients experiencing a drop in the platelet count at the time of initial diagnosis. 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%).

3.5. 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 23mg/L (<1-250mg/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 $108x10^9$/L ($13-289x10^9$/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 intra-luminal 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 8 cases, thickened, aperistalsic bowel with an extra-luminal fluid collection, highly suspicious of an intestinal perforation, was identified.

Seventeen patients underwent laparotomy with a median time to surgery of 2 days (1-5) from the date of first suspicion of NEC. Findings at surgery were: localised distal ileal disease with perforation in 9 (52.9%), multi-focal 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 post-operative 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%).

4. DISCUSSION

We report our experiences and outcomes of babies born <24 weeks of gestational age over a period of 6 years, with a 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 numbers of babies with any degree of IVH was higher within the NEC cohort, however the numbers 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 (1–6). 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 (18). 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 (15–17,19). This progress was backed up by the National Institute of Child Health and Human Development (NICHD)-funded Neonatal Research Network (NRN), reporting survival rates of 25% for babies born at 22 weeks (20). 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 an detrimental impact in terms of outcome when compared to our control cohort.

A protective effect of maternal breast milk on development of NEC has been described previously (21,22). 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 $MgSO_4$ on the risk of developing NEC. Some studies have reported a positive association, especially in infants of very low gestational age (10,11) whilst others report a protective effect (23). The findings in our cohort were of a higher proportion of controls (no diagnosis of NEC) receiving both $MgSO_4$ and maternal breast milk compared to 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 $MgSO_4$ 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 (24). 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 multi-focal.

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) 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 six years. The 56 infants included, is 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 interrelated 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 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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What is already known on this topic:

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, IVH, or PVL. Surgery should therefore be offered, when indicated, for this most vulnerable cohort.

How this study might affect clinical practice:

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 BAPM 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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