**Title page**

**Emergency laparotomy in infants born at <26 weeks gestation: a neonatal network based cohort study of frequency, surgical pathology and outcomes**

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Word count

**Abstract**

**Objective**: identify the proportion of infants born at <26 completed weeks gestation that require emergency laparotomy and review the surgical pathology, incidence of subsequent surgical procedures, and outcome

**Design**: retrospective cohort review

**Setting**: tertiary neonatal surgical unit

**Patients**: all infants born at < 26 weeks gestation in a neonatal network over an 8 year period

**Results**: Of 381 infants, laparotomy was indicated in 61 (16%) and performed in 57. Surgical pathology encountered included spontaneous intestinal perforation (28), necrotising enterocolitis (NEC) (14), volvulus without malrotation (1), strangulated inguinal hernia (1), milk curd obstruction (4), NEC stricture (1) and meconium obstruction of prematurity (2). No intestinal pathology was found in six. Four infants with indications for laparotomy and severe comorbidity had intensive care withdrawn without surgery. The most frequent procedure performed was resection with primary anastomosis. Nine infants (16%) required more than one laparotomy. Of the 16 infants who had stoma formation 8 had closure before discharge. Fifteen infants required surgical patent ductus arteriosus ligation following laparotomy and 17 had laser therapy for retinopathy of prematurity. Overall 42 infants with indication for laparotomy (69%) survived to discharge.

**Conclusions**: Nearly one in six infants born at < 26 weeks required emergency laparotomy. The most frequent pathology encountered was spontaneous intestinal perforation (49%) followed by NEC (25%). Over one quarter required subsequent gastrointestinal surgery with many also requiring cardiothoracic and ophthalmic procedures. These data are important for those caring for extremely preterm infants, the provision of information to parents, and organisation of neonatal services.

Keywords: extreme prematurity, necrotising enterocolitis, surgery, outcome, intestinal perforation

**Introduction**

Premature infants are prone to a number of acquired pathologies that may require surgery including significant intestinal complications such as NEC [1-4] and spontaneous intestinal perforation (SIP).[5] With the increase in survival of infants born at extreme prematurity (defined as birth at less than 26 weeks completed gestation [6]) more infants are surviving to develop these intestinal complications. Large epidemiological studies report the incidence of infants requiring surgery for NEC in this group of infants as 7-8% [3,6] but NEC is only one of a number of conditions associated with prematurity that may require emergency laparotomy.

Data regarding the frequency of surgical pathology affecting infants born at extreme prematurity is important for clinicians caring for preterm infants, to provide parents with accurate information and for planning health care provision. We aimed to determine the incidence of intestinal pathology requiring surgical review, interventions required, pathology encountered, and outcomes to time of neonatal discharge in infants born at <26 weeks gestation in our neonatal network.

**Methods**

The neonatal surgical service in the Thames Valley and Wessex Neonatal Network (Wessex) is based in a combined neonatal medical and surgical intensive care unit. There are approximately 33,000 live births annually in this network which contains two level 3 neonatal intensive care units (NICUs) and seven local neonatal units. The regional neonatal surgical service is based in one of the NICUs. A retrospective network-based cohort study was undertaken of all babies born at less than 26 weeks completed gestation who were reviewed by the neonatal surgical team during an 8 year period between April 2007 and March 2015. Patients were identified from a prospectively maintained neonatal surgical database and included in this study if they were reviewed by a general neonatal surgeon; those referred for cardiac, neurosurgical or ophthalmology conditions were excluded. Babies born outside of our neonatal network admitted for surgery were excluded but babies born in network following in utero transfer from other networks were included. Any baby discharged and subsequently readmitted to our service was counted once only. Since this was a retrospective cohort study, there was no intervention as part of the study.

During the study period indication for laparotomy was as determined by the consultant surgeon and neonatologist in charge of the infant’s care. For infants with NEC this was largely in keeping with generally accepted indications. [7] The diagnosis of SIP as distinct from NEC was made on the basis of radiology (the lack of pneumatosis or portal gas on abdominal radiographs) and macroscopic appearance at laparotomy (focal perforation in otherwise entirely normal intestine lacking any external signs of inflammation). Previous studies have shown that the ability to distinguish between NEC and SIP at surgery is high. [8]

The total number of live births in the network at less than 26 weeks gestation was obtained from the neonatal network database. The study has received institutional approval and data was recorded from neonatal discharge summaries, histopathology and radiology reports, and operation notes. The final diagnosis for each infant was that assigned to them by the consultant in charge of their care during their treatment episode on the basis of clinical and surgical features. Data are expressed as median (range).

**Results**

There were 381 infants born < 26 weeks within the neonatal network during the study period. There were no transfers out of network for intestinal surgical problems. Eighty six infants (23% of births) had surgical review by our service. In 61 infants (16% of births, 71% of referrals) there were indications for emergency laparotomy. Surgical intervention was felt to be inappropriate in 4 infants with multiple organ dysfunction syndrome and severe co-morbidity. All had intensive care withdrawn and died. The 57 babies who underwent a laparotomy had a median gestational age of 24+6 weeks (23+1 - 25+6) and median birth weight of 660g (430 – 1000). None of the infants had insertion of a peritoneal drain either as a temporary or definitive procedure. The pathologies encountered at laparotomy are presented in Table 1. Presentation occurred at an earlier age in infants with SIP, 9(5-54) days, compared to NEC, 36(8-55). Details of the other 25 referrals to the surgical service are shown in Table 2.

Procedures performed at laparotomy are detailed in Table 1. The most frequent procedure performed was intestinal resection with primary anastomosis in 29 infants (51%). A stoma was fashioned in 16 (28%). Nine infants (16%) underwent at least one additional laparotomy prior to hospital discharge for acute pathology (Table 3), the primary diagnosis having been spontaneous intestinal perforation (SIP) (5), NEC (3), and milk curd obstruction (MCO)(1).

Prior to discharge, a total of eight infants had closure of their stoma on a non-acute basis; the remaining 8 infants with a stoma still had it at discharge home.

Whilst reviewing the medical records of these infants we noted non-abdominal surgical intervention was frequently required in these infants requiring laparotomy. Of the 57, 15 (26%) underwent PDA ligation following laparotomy and 17 of the 42 infants who survived (41%) had laser therapy for retinopathy of prematurity (ROP).

Overall mortality prior to discharge in those with an indication for laparotomy was 30% (18/61 infants). In those who underwent laparotomy the mortality was 25% (14/57), death occurring at 14 (0-66) days after surgery. One patient died immediately after surgery with total intestinal NEC. Death in the remainder, who had survived the immediate post-operative period, was as a result of re-orientation of care due to multi-organ failure (7), respiratory failure (4) and recurrent inoperable NEC (2). Mortality rates by diagnosis are shown in Table 1. Median length of stay (from birth to hospital discharge) in those who survived to discharge was 123 (78-181) days.

**Discussion**

One of the primary aims of this study was to determine the proportion of infants born at <26 weeks gestation who will require emergency laparotomy. Previous publications report 10-12% of infants with birth weight <1000g requiring laparotomy for NEC or SIP.[9,10] The EPICure2 study, a recent large UK prospective study of infants born at <26 weeks, reported that surgery for NEC was required in 8%.[6] Similarly a large study from the USA reported surgery for NEC in 7% of infants <26 weeks.[3] However NEC is only one of a number of conditions that may require emergency laparotomy in infants of this gestation.[11-14] To our knowledge, this is the first study to identify the overall incidence of emergency laparotomy reporting the full breadth of surgical intestinal pathology in infants born at <26 weeks. In our neonatal network nearly one quarter (23%) of the infants in this gestation group were referred for neonatal surgical review. The majority of referrals were for intestinal complications or dysfunction associated with prematurity and overall, 16% (nearly 1 in 6) of all infants born at < 26 weeks had an indication for laparotomy.

 The most frequently encountered pathology at laparotomy was SIP which was encountered at twice the frequency of NEC. These relative incidences are similar to those reported by Eicher in infants born at <1000g.[9] Whilst there has been debate about the distinction between NEC and SIP [12], most authors now agree that these are distinct entities. SIP tends to present at an earlier gestational and postnatal age than NEC [15] and with a differing biomarker profile.[16,17] Although NEC is a much feared complication of prematurity and is the intestinal complication most frequently reported in the context of the preterm infant, our results clearly demonstrate that NEC is just one of a number of intestinal pathologies that may require laparotomy in this population. It is unclear whether reporting of NEC in large epidemiological studies [3,18-20] also includes infants with SIP or indeed the other pathologies we have encountered here and reported previously.[11,13] These studies frequently make no mention of SIP. Our data demonstrates that SIP is in fact encountered more frequently than NEC at laparotomy and therefore studies that report solely NEC may be significantly underestimating the intestinal consequences of extreme prematurity. We believe that there is justification in demanding that all reports including gastrointestinal complications of prematurity report SIP and NEC as separate entities. By not reporting SIP there is a risk that an important cause of morbidity and mortality is overlooked. We support ongoing initiatives to create a Core Outcome Set in this field and anticipate that this will enhance standardisation of outcome reporting. [21]

Following initial laparotomy a high proportion of infants (44%) required subsequent gastrointestinal surgery. This was either emergency laparotomy for further acute intestinal pathology, or stoma closure. We have previously highlighted a high incidence of further intestinal pathology following laparotomy for SIP [22] which accounted for the majority of these cases.

In addition to further gastrointestinal surgery, other surgical intervention was required in a high proportion of those requiring laparotomy. Over one quarter of infants who survived laparotomy subsequently had a PDA ligation and 41% required laser treatment for ROP. This need for further intervention is notably higher than reported in epidemiological studies; in EPICure2, PDA ligation and ROP treatment were both performed in 16% of extremely preterm infants.[6] In the French EPIPAGE2 epidemiological study the incidence of ROP treatment was 8.3% in this population.[18] The higher need for PDA ligation in our series may be due to a reluctance to treat a PDA medically following laparotomy for intestinal pathology. We suspect that the higher need for all interventions, including laparotomy, is a reflection of multiple co-existing, likely related, morbidities in this subset of extremely preterm infants.

Overall mortality in infants with an indication for laparotomy was 27%. Whilst this is lower than the mortality attributed to just NEC in extremely preterm infants in some other series [1] the number of cases in our series is relatively small and our cohort includes babies with diagnoses other than NEC who may be predicted to have better outcomes. However, 1 in 4 infants who survived laparotomy did not survive to neonatal discharge.

An interesting observation in performing this study was that none of the infants in this cohort with NEC referred for surgical assessment during the study period avoided laparotomy. It is possible however that not all infants were referred for assessment since a recent study has shown that approximately 20% of infants born at <32 weeks gestation who die from NEC do so without a laparotomy.[19]

These observations have implications for parental counselling, service delivery and resource use. We believe parents should be informed about the high chance of their child needing a laparotomy during the perinatal period just as they are regarding other complications of prematurity. Some may argue that the high demand for surgical intervention in this population should mandate that all extremely preterm infants are born and cared for in units with neonatal surgeons. Transfer to a neonatal surgeon for assessment and treatment could then be avoided. Such an approach would require significant alterations in the delivery of neonatal care since currently many level 3 NICUs do not have on-site neonatal surgical expertise. However, existing data support the concept of centralisation such as this with a recognised relationship between birth and subsequent care in a level 3 NICU [23] or high-volume NICU [24] and improved outcomes for preterm infants. Finally the high requirement for further surgical intervention could be used as an argument for infants who have had a laparotomy remaining in a unit with neonatal surgical (general, cardiothoracic and ophthalmology) expertise until discharge.

**Conclusion**

Nearly 1 in 6 infants born at < 26 weeks gestation require laparotomy for acute intestinal pathology which encompasses a range of disorders, rather than solely NEC. Following laparotomy there is a high requirement for further surgery including repeat laparotomy in 16%. This information will be valuable for health professionals involved in the care of babies born at extreme prematurity and will aid in the provision of information to parents regarding the possible outcomes for babies born so early. It acts as a reminder to clinicians caring for preterm babies that a range of intestinal pathologies may require surgical treatment and will be valuable in assessing healthcare delivery requirements and resources for this group of patients.

**Acknowledgements**

NJH is supported by the National Institute for Health Research through the NIHR Southampton Biomedical Research Centre.

The authors have no competing interests and received no funding for this work

What is already known on this issue:

* Surgery for necrotising enterocolitis is required in 8% of infants born at extreme prematurity
* NEC is only one of a number of intestinal pathologies found in such infants

What this study adds

* Emergency laparotomy is required in 16% of infants born at < 26 weeks gestation
* Necrotising enterocolitis accounts for only 25% of pathology encountered
* Further surgery, including abdominal, PDA ligation and retinopathy surgery are frequently required

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**Tables**

|  |  |  |  |
| --- | --- | --- | --- |
| **Diagnosis** | **n****(%)** | **Procedure performed** | **Mortality****n (%)** |
| SIP | 28(49) | Resection and primary anastomosis (15)Resection with stoma formation (7)Stoma formation without resection (6) | 9(32) |
| NEC | 14(25) | Resection and primary anastomosis (10)Resection with stoma formation (1)Open and close (1)Clip and drop (1)Stoma formation without resection (1) | 6(43) |
| Milk curd obstruction | 4(7) | Enterotomy and washout (2)Stoma formation without resection (1)Resection and primary anastomosis (1) | 2(50%) |
| No intestinal pathology\* | 6(11) | Diagnostic laparotomy (6) | 0 |
| MOP | 2(4) | Enterotomy and washout (2) | 0 |
| Strangulated inguinal hernia | 1(2) | Resection and primary anastomosis, hernia repair | 0 |
| NEC stricture | 1(2) | Resection and primary anastomosis | 0 |
| Volvulus without malrotation | 1(2) | Resection and primary anastomosis | 1 |

\* Final diagnosis: sepsis (n=2), parental nutrition extravasation (2), no cause identified (2).

NEC – necrotising enterocolitis; SIP – spontaneous intestinal perforation; MOP – meconium obstruction of prematurity

**Table 1: Diagnoses encountered, procedures performed and mortality in 57 infants who underwent laparotomy.**

|  |  |
| --- | --- |
| **Diagnosis** | **n** |
| Need for surgical central venous catheter | 3 |
| Inguinal hernia  | 3 |
| Oesophageal atresia | 1 |
| Vascular complicationsCentral line extravasation injury (1)Fractured umbilical arterial line (1) | 2 |
| Anorectal anomaly | 1 |
| Septic ileus | 7 |
| MOP relieved by rectal irrigation | 6 |
| Feed intolerance | 2 |

MOP – meconium obstruction of prematurity

**Table 2: Indication for surgical review in 25 infants in whom emergency laparotomy was not indicated**

|  |  |
| --- | --- |
| **Indication** | **n** |
| Further bowel perforation (initial diagnosis SIP) | 5 |
| Adhesional bowel obstruction | 1 |
| Anastomotic leak | 1 |
| NEC (initial diagnosis SIP) | 1 |
| Re-look laparotomy for NEC | 1 |

NEC – necrotising enterocolitis; SIP – spontaneous intestinal perforation

**Table 3: Indications for re-laparotomy prior to discharge (n=9)**