Impact of Transfer for Surgical Management of Preterm Necrotising Enterocolitis or Focal Intestinal Perforation

Claire L. Granger [a, b], Kunal Mukherjee [a], Nicholas D. Embleton [a, c], Robert J. Tinnion [a], Janet E. Berrington [a, b], *

[a] Neonatal Intensive Care Unit, Royal Victoria Infirmary, Newcastle-upon-Tyne Hospitals (NuTH) NHS Trust, Newcastle, NE2 4BJ, United Kingdom
[b] Translational and Clinical Research Institute, Newcastle University, Framlington Place, Newcastle, NE2 4HH, United Kingdom
[c] Population Health Sciences Institute, Newcastle University, Framlington Place, Newcastle, NE2 4HH, United Kingdom

ARTICLE INFO

ABSTRACT

Objective: To compare outcomes after surgically managed necrotising enterocolitis (NEC) and focal intestinal perforation (FIP) in infants <32 weeks requiring transfer to or presenting in a single surgical centre.
Design: Retrospective review of transferred and inborn NEC or FIP, from January 2013 to December 2020.
Patients: 107 transfers with possible NEC or FIP contributed 92 cases (final diagnoses NEC (75) and FIP (17)); 113 inborn cases: NEC (84) and FIP (29).
Results: In infants with a final diagnosis of NEC, medical management after transfer was as common as when inborn (41% TC vs 54% p = 0.12). Unadjusted all-cause mortality was lower in inborn NEC (19% vs 27%) and FIP (10% vs 29%). In infants undergoing surgery unadjusted mortality attributable to NEC or FIP was lower if inborn (21% vs 41% NEC, 7% vs 24% FIP). In regression analysis of surgically treated infants, being transferred was associated with increased all-cause mortality (OR 2.55 (1.03–6.79)) and mortality attributable to NEC or FIP (OR 4.89 (1.80–14.97)).
Conclusions: These data require replication, but if confirmed, suggest that focusing care for infants at highest risk of developing NEC or FIP in a NICU with on-site surgical expertise may improve outcomes.

© 2023 Elsevier Inc. All rights reserved.

1. Introduction

Necrotising enterocolitis (NEC) or focal intestinal perforation (FIP) occur in around 10% of infants born <32 weeks gestation [1] and many require surgical assessment. Many at-risk infants are in a tertiary level neonatal intensive care unit (NICU) when disease presents, but some will not have on-site surgical expertise and require transfer, potentially whilst seriously unwell. A minority present in lower acuity special care units (SCU). These infants also require transfer for surgical assessment.

In the UK treatment for FIP is almost universally surgical [2], and difficulty remains in differentiating NEC and FIP [3,4]. Infants with recognised perforation require immediate transfer to a surgical centre but it is less easy to define the optimal transfer window in those with more insidious disease [5–8] and thresholds for transfer vary [9]. Transfer of the critically ill patient is associated with

significant risk and is known to increase morbidity and mortality in other patient groups (Sampalis 1995, Fan 2006).

Surgical NEC is associated with up to 50% mortality [10,11] and FIP with a 20% mortality [12,13]. Infants who survive NEC or FIP have prolonged hospital stays, potential long term parenteral nutrition, and an increased risk of neurodevelopmental complications [11,14].

Predictive factors for outcome after NEC suggest gestation is most important [15] but there are few data on whether outcomes differ depending on need for transfer to a surgical centre, and what may affect any differences. Two previous studies in the USA and Australia did not find an association between mortality and transfer for NEC [16]. We could not identify any similar data for infants with FIP, nor literature distinguishing transfer with known perforation from that without.

The Northern Neonatal Network covers an area of ~12,000 km^2 and a population just over 3 million. There are 12 neonatal units comprising three tertiary-level NICUs (one of which provides neonatal surgery), no level 2 units and seven level 1 units (prior to 2018 one of the level 1 units was a NICU). Since 2016 there has been a single regional transport team (Northern Neonatal Transport Service, NNeTS), co-located with the surgical NICU. Before this, two

unit-based teams undertook transfers (one in the North and one in the South). Travel times to the surgical NICU from across the region are 20−120 min (Fig. 1).

As neonatal networks continue to develop and reconfigure, and to guide decisions around optimal location of care for highest risk infants, we aimed to determine case mix, management and outcomes for infants likely to require abdominal surgery for NEC and FIP, and compare differences between infants requiring transfer to the surgical centre (transferred cases, TC), with those presenting at the surgical centre (inborn). We also attempted to identify the number of cases with NEC neither referred to nor actually transferred to the surgical centre (non transferred cases (NTC)).

We hypothesised that there would be a difference in outcomes between infants with NEC or FIP presenting in a non-surgical centre and referred for transfer, compared to those presenting in a surgical neonatal unit.

2. Methods

2.1. Case identification

2.1.1. Transferred cases (TC)

Referrals for possible NEC or perforation with birth gestation <32 weeks, transferred to the surgical centre between January 2013 to December 2020 were identified from a manual search of the transport service database, cross-checked with electronic case records (BadgerNet™), the surgical unit research database and hospital coding lists for NEC and FIP to ensure all cases were identified. To the best of our knowledge during the study period no infant was referred to the regional centre but actually transferred out of region and no infant referred directly out of region.

2.1.2. Inborn cases

Infants with a diagnosis of NEC or FIP who presented in the surgical unit were identified for the same period using the same cross-checking approach.

2.1.3. Non transferred cases (NTC)

Network data in BadgerNet™ was interrogated to identify total regional admissions with birth gestation <32 weeks and total regional NEC cases. This cross check with total regional NEC cases was undertaken in a bid to ensure that NEC cases were not being missed from this study (i.e occurring and not being referred for potential transfer).

2.1.4. Data collection

Demographic and outcome data (gestation, birthweight, feed type, gender, time to full feeds, antenatal steroid receipt, mortality prior to discharge from neonatal care, cause of death) were extracted from electronic records and transport specific data (postnatal age, clinical condition at referral, referral diagnosis, management before transfer) from transport database.

2.1.5. Case classification/definitions

British Association of Perinatal Medicine (BAPM) levels of care were used and transfer classifications are as defined by BAPM and the Neonatal Transport Group (NTG) [17,18] and constitute: time critical − departure should be within 1 h of the start of the referral call; stabilisation time: time from arrival at referral unit to departure. All cases were reviewed by two independent clinicians (CG, JB) using definitions previously published [3,19]. NEC and FIP were classified using all available information including histology to differentiate the two [3]. Surgical NEC (NECS) was confirmed at laparotomy (clinically and histologically where resection occurred). In infants who died before surgery classification as NECS required a definitive diagnosis of NEC. Death directly attributable to NEC or FIP was defined as NEC or FIP being the primary certified cause of death. Combined moderate or severe neurodevelopmental impairment at two years was defined by delay in development of at least 6 months as determined by the Bayleys scale of infant development.
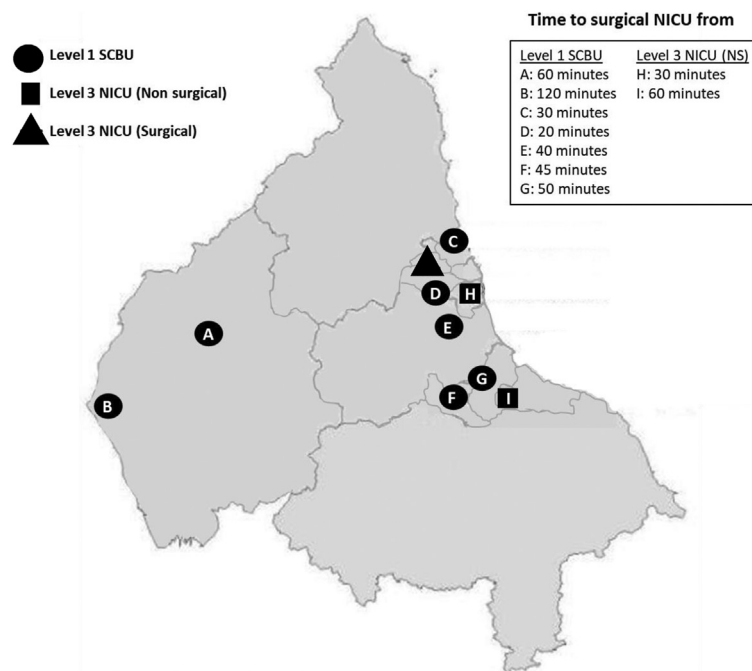

Fig. 1. Map of Northern Neonatal Network showing location of neonatal services and geographic region covered by NNeTS.

2.2. Statistics

Statistical analysis used GraphPad Prism. Mann–Whitney U test was used to determine differences between non-parametric data, and χ2 test to analyse differences in frequencies between cohorts. Logistical binomial regression analysis was undertaken, firstly with a univariate model, then subsequently using a multivariate model to adjust for confounding factors.

3. Results

3.1. Transferred infants

107 infants were transferred with a relevant suspected diagnosis: perforation (either NEC or FIP (22), NEC without perforation (66) or abdominal symptoms without specific diagnosis from referral team (19)) (Table 1). No infant died after referral but before transfer. 92 had a final diagnosis of NEC (75) or FIP (17), and 15 had non-surgical diagnoses. All 22 infants considered to have perforated at referral had this confirmed at laparotomy, and an additional 13 cases were identified at laparotomy.

3.2. Stabilisation and transfer

23% (25/107) of all referrals were categorised as time critical at referral (for suspected perforation (16) or cardiorespiratory deterioration (9)) and target time to retrieve was met for all. Stabilisation time was significantly longer for infants referred with suspected perforation compared with other referral diagnoses (p = 0.02), and these infants more frequently were receiving invasive ventilation and inotropic support (Table 1).

3.3. Inborn NEC and FIP infants

In the same period, 84 inborn infants were diagnosed with NEC, and 29 with FIP.

3.4. Network data

In the same period BadgerNet™ identified 2961 admissions <32 weeks alive at 48 h and eligible for NEC outcomes across the network and a total of 79 regional NEC cases were recorded in BadgerNet.

3.5. Demographics of transferred and inborn NEC and FIP infants

Demographics are shown in Table 2 by final diagnosis. Inborn infants with NEC were born at a lower gestational age (and had lower birthweight) and presented earlier than TC but other demographic factors were similar. FIP cases were similar demographically whether inborn or transferred. Receipt of maternal milk differed significantly with inborn cases of both types, being more likely to receive maternal milk. One infant in both the inborn and outborn cohorts had major congenital cardiac disease (one hypoplastic left heart syndrome, and one tricuspid atresia) and one inborn infant had an antenatally diagnosed congenital diaphragmatic hernia.

3.6. Management of NEC and FIP

59% transferred NEC underwent a laparotomy, compared to 46% of inborn NEC (p = 0.12). For transferred cases with surgical NEC (NECS), time from symptoms to referral was less than 24 h in 80%; for the remaining 20% median time to referral was 6 days (IQR 2–10)). Pan-enteric disease was seen in 25% of transferred NECS infants compared to 5% inborn NECS (p = 0.08), and all infants with pan-enteric NEC were palliated. An additional three transferred NECS infants received palliative care due to clinical deterioration before (2) or during (1) laparotomy; this did not occur in inborn cases. Median resection length in transferred non pan-enteric surgical NEC was 11 cm (IQR 5–40 cm) compared to 10 cm (IQR 5–15 cm) for inborn NEC (Table 3).

Of the 25 infants transferred as time critical 21 (84%) underwent laparotomy within 24 h, compared with 31% (21/87) of those non time critical transfers (p < 0.01). Most (83%) transferred infants with a final diagnosis of FIP were referred less than 24 h after onset of symptoms, and the remaining three infants were referred at two, two and four days respectively. After transfer time to surgery from arrival was <24 h in 75% infants with final diagnosis of NECS and 88% with final diagnosis of FIP. In inborn infants time to surgery from diagnosis was <24 h in 49% NECS and 90% FIP (Table 3).

3.7. Outcomes

26 (24%) of all transferred cases died. Final diagnoses for the referral episode in transferred non-survivors were NEC (20), FIP (5) and late onset sepsis (LOS) (1). For infants with a final diagnosis of NEC or FIP unadjusted all-cause mortality was lower in inborn infants (19% vs 27% NEC, 10% vs 29% FIP) as was unadjusted death directly attributable to NEC (21% vs 41%) or FIP (7% vs 24%) (defined as the primary certified cause of death) and this attributed mortality was statistically significantly higher in transferred cases in unadjusted analysis (Table 3). Infants who were transferred and died of NEC or FIP were exclusively from non-surgical tertiary units, and not level 1 units. For surgically managed infants only, in regression analysis adjusted for gestation, sex, mode of delivery, antenatal steroid receipt, breast milk receipt at full feeds and during or prior to establishment of the neonatal network, being transferred significantly impacted both all-cause mortality (OR 2.55 (95% CI 1.03–6.79)) and mortality attributable to NEC or FIP (OR 4.89

Table 1
Referral and transfer.

Median and IQR or n (%)	Referral diagnosis			p value (perforated compared with NEC and other)
	Perforation (FIP or NEC) (22)	NEC (not perforated) (66)	Abdominal concerns (other) (19)	
Referred by Level 3 unit (%)	**21 (95)**	**46 (70)**	**11 (58)**	**<0.01**
Suspected perforation at referral (%)	22 (100)	0	0	n/a
Time critical (%)	**22 (100)**	**3 (5)**	**0**	**<0.01**
Stabilisation time, minutes (IQR)	**99 (65–120)**	**83 (59–93)**	**69 (60–80)**	**0.02**
Intubated at point of referral (%)	**19 (86)**	**31 (52)**	**10 (59)**	**<0.01**
Intubated for transfer (%)	**21 (95)**	**46 (70)**	**10 (59)**	**<0.01**
Inotropic requirement (%)	**8 (36)**	**5 (8)**	**0**	**<0.01**

bold value indicates significant difference

Table 2
Demographic information.

Final diagnosis	NEC (159)						FIP (46)	
Median and IQR or n (%)	Total		NECS		NECM		Inborn (29)	TC (17)
	Inborn (84)	TC (75)	Inborn (39)	TC (44)	Inborn (45)	TC (31)		
Gestation	26 (24.5–27.4)	27.1 (25–28.7)	25.7 (24.4–25.7)	26.9 (24.6–28)	26.9 (24.6–27.8)	28 (26.3–29.4)	26.1 (24.3–29.4)	26 (24.2 27.2)
≥28w	15 (18)	29 (39)	6 (15)	12 (27)	9 (20)	17 (55)	9 (31)	3 (18)
≤28w	69 (82)	46 (61)	33 (85)	32 (73)	36 (80)	14 (45)	20 (69)	14 (82)
Birth weight	800 (620–910)	917 (673–1370)	800 (630–930)	819 (660–1027)	845 (625–980)	1100 (740–1370)	869 (716–1213)	908 (617–1073)
Male	55 (65)	50 (67)	26 (67)	24 (55)	29 (64)	19/31 (61)	23 (70)	11 (61)
Day of onset of symptoms	17 (12–30)	24 (14–33)	16 (12–23)	19 (12–27)	23 (14–37)	28 (20–35)	3 (3–8)	4 (2–10)
Mode of delivery - CS	39 (44)	43 (57)	18 (46)	22 (50)	21 (47)	18/31 (58)	12 (40)	5 (29)
Antenatal steroids	80 (95)	72 (96)	37 (94)	42 (95)	45 (100)	30/31 (97)	28 (95)	14 (82)
Probiotics pre disease	65 (77)	28 (37)	26 (66)	17 (39)	39 (87)	11 (35)	10 (34)	2 (12)
Day of life of initial milk (IQR)	3 (2–4)	3 (1–4)	3 (2–4)	3 (2–4)	3 (2–3)	2 (1–3)	4 (2–5)	7 (2–9)
Maternal milk at full feeds (any)	75 (89)	52 (70)	32 (82)	26 (59)	43 (96)	26/31 (84)	24 (83)	4 (23)
Maternal milk fed at full feeds (exclusive)	55 (68)	34 (45)	26 (67)	20 (45)	29 (64)	14/31 (45)	16 (55)	3 (18)
Maternal milk at disease (any)	66 (83)	44 (59)	28 (72)	26 (59)	38 (84)	18/31 (58)	22 (76)	10 (59)
Maternal milk at disease (exclusive)	57 (68)	26 (35)	26 (67)	17 (39)	28 (62)	9/31 (29)	18 (62)	10 (59)

Bold denotes p < 0.05.

Table 3
Management and outcomes.

Final diagnoses	NEC (n)		FIP (n)	
n (%) (95%CI)	Inborn (84)	TC (75)	Inborn (29)	TC (17)
Medical management only	45 (54) [44–65]	31 (41) [32–54]	—	—
Surgical management	39 (46) [37–58]	44 (59) [49–71]	29	17
Median bowel resection length in cm (IQR)[a]	10 (5–15)	11 (5–43)	—	—
Pan-NEC	4/39 (5) [4–26]	11/44 (25) [15–42]	—	—
Mortality (all cause) (%)	16/84 (19) [12–30]	20/75 (27) [18–39]	3 (10) [4–30]	5 (29) [14–61]
Mortality attributable to NECS or FIP (%)	**8/39 (21) [11–38]**	**18/44 (41) [29–58]**	2 (7) [2–26]	4 (24) [10–55]
Neurodevelopmental impairment at two years[b] (%)	15/36 (42) [28–61]	3/13 (23) [9–62]	4/15 (27) [12–62]	2/5 (40) [14–67]
Neurodevelopmental impairment or death at two years[b] (%)	28/49 (57) [45–73]	23/33 (70) [56–87]	8/19 (42) [25–71]	7/10 (70) [47–86]

Bold denotes p < 0.05.
[a] Pan-NEC excluded.
[b] Moderate or severe neurodevelopmental impairment (at least 6 months delay) in survivors for whom data available (data not available or infants too young in some cases).

Table 4
Regression analysis showing adjusted odds ratios (aORs) for mortality for surgical NEC and FIP infants.

	Surgical NEC and FIP (combined) aOR (95% CI) (p)		
		All-cause mortality	NEC or FIP related mortality
Cohort	TC versus inborn	**1.54 (1.03–6.79) (0.03)**	**2.4 (1.14–5.32) (0.02)**
Gestation at birth	Each additional week	**0.27 (0.11–0.87) (0.01)**	0.88 (0.72–1.05) (0.17)
Female	Versus male	**0.51 (0.11–0.61) (0.04)**	0.62 (0.29–1.33) (0.22)
Breastmilk at full feeds	Yes versus no	0.67 (0.28–1.55) (0.35)	1.01 (0.34–3.22) (0.99)
Delivery mode	Vaginal versus caesarean	1.33 (0.53–3.40) (0.54)	1.84 (0.83–4.17) (0.13)
Antenatal steroids	Yes versus no	0.95 (0.19–3.91) (0.95)	0.61 (0.12–3.49) (0.55)
Neonatal Network	Yes versus no	1.39 (0.31–6.04) (0.65)	

Bold denotes p < 0.05.

(95% CI 1.80–14.97)), (Table 4). Infants who died were of the same median gestation and birthweight whether transferred or inborn. Original classification of the referral as time critical or not did not impact mortality (48% vs 37% p = 0.46). In six infants referred with NEC more than 24 h after symptom onset mortality was 50%, in contrast to 29% in infants referred within 24 h of symptom onset.

4. Discussion

4.1. Summary

We present the first UK data from a geographically defined population of preterm infants with NEC or FIP evaluating the impact of requiring transfer for surgical involvement and show important differences in outcomes compared to inborn infants. NEC infants requiring transfer were of a higher gestation (and birthweight), with later presenting disease and were less likely to receive breast milk. Transferred infants were more likely to have pan-enteric disease and had higher mortality due to NEC or FIP after adjustment for potential confounders. FIP infants were similar demographically in both groups, but transferred infants still had higher mortality. All transferred infants with NEC or FIP attributable deaths were transferred from a level 3 unit. Stabilisation and transfer timing and duration were in keeping with national guidance [17].

4.2. Comparison to published literature

In surgical NEC all-cause mortality was 43% and 38% in transferred and inborn cases respectively which compare to global meta-analysis average surgical mortality of 34.5%, (95% CI 30.1–39.2) [11] and UK all-cause mortality after severe NEC of 48.1% [20]. Many studies do not separately report mortality directly attributable to NEC, but we identified differences in disease attributable mortality of 21% and 41% for inborn and transferred surgical NEC infants respectively. An American study comparing risk adjusted mortality after NEC in VLBW infants born in level 3 equivalent units without surgical capacity identified an odds ratio (OR) for mortality of 1.5 compared to units with surgical capacity [21]. Worse composite outcomes (death or NEC) in infants with very low birthweights born in NICUs with lower volume of patients or lower defined level of care has also been shown [22]. In contrast, adjusted mortality was not statistically different depending on need for transfer in infants with surgical NEC in America (OR for death 0.75, 95% CI 0.42–1.32) [16] and Australia (OR for death 0.69 (95% CI0.32 to 1.51)) [10].

4.3. Strengths and limitations

This study utilised detailed knowledge of demographic factors and application of standard definitions with adjustment for many confounders. However, we did not have information on some factors that may impact both NEC incidence and severity such as antibiotic exposure [23], transfusion practices [24], or delayed cord clamping [25].

We also did not have good data for infants with NEC or FIP that were never referred to the regional surgical centre. Using BadgerNet™ to try to identify these never referred infants we identified fewer babies with NEC regionally (79) than were already known to us in this study (159). During this period 2961 infants < 32 weeks were cared for regionally. Regional medical and surgical NEC rates combined are thus 6.8% and surgical NEC rates 3.5% using infants identified in this study and 1.9% using National Neonatal Research Database (NNRD) identified cases. These compare to the severe NEC rates identified nationally by region of 2.51%–3.85% [26]. Our data include infants born at <32 weeks' gestation, however we recognise that a small proportion of infants born at greater than this develop NEC, but presentation and referral pathways may differ. The never-referred group may include stable babies, and we acknowledge that identification of these data through BadgerNet may be under-quantified or inaccurate. Infants who died prior to laparotomy are included in inborn data, but may not be represented in the transferred cases, and thus this does not obviously explain the observed mortality differences in NEC which are in favour of being inborn.

There may be a degree of unconscious bias as the authors work in the tertiary surgical centre, however all efforts were taken to mitigate against this by review of cases by two independent clinicians (CG and JB)) and reviewed by a third (RT) if there was any disagreement.

4.4. Meaning and future studies

Diagnosis and management of NEC and FIP remains challenging and optimal management strategies unknown. Timely surgical intervention in those infants who require laparotomy is important for improving outcomes, but data are limited. Our data suggest a difference in the nature of NEC in transferred infants, with more pan-enteric disease and worse outcomes. Given the incomplete understanding of pathophysiology of NEC this may be due to differences in antecedent factors in transferred cases, possibly resulting in a difference in NEC presentation or progression. We did identify differences in maternal milk receipt and probiotic receipt in transferred versus inborn cases, but existing literature does not suggest these impact on NEC presentation or severity, or the likelihood of pan-enteric disease. Other practices that may be anticipated to impact on NEC phenotype are similar across the network including oxygen saturation targets, feeding regimes, and involvement in collaborative nutrition trials. Similarly transfer itself has not previously been associated with specific surgical findings or outcomes. Transfers themselves met criteria for dispatch and no infant died during transfer.

These data raise important issues. Validation of these findings nationally could be undertaken through the NNRD given efforts that have been undertaken to validate NEC diagnoses within National Neonatal Audit Programme (NNAP) recently. Centralised transport services could contribute to ensuring that all transferred cases are identified, and surgical databases to identifying those with final diagnoses of NEC or FIP, making a national approach to answering this question feasible.

All transfers met national standards for time to referring unit and stabilisation, however despite this, there was an increased mortality in those infants born in a non-surgical centre. Additional more difficult to measure factors may also contribute to outcomes. These may include familiarity and experience of staff with surgical neonates impacting recognition of conditions like NEC and impacting on time to surgical intervention. These could potentially be modified with outreach/network education work.

If these findings were corroborated, the data suggest that a centralised approach that cares for infants at the highest risk of developing NEC or FIP in a NICU with on-site surgical expertise may reduce mortality and improve outcomes. Implications for service delivery would not be insignificant. Transferred NEC infants had a median gestation at birth of 27.1 weeks (IQR 25–28.7) and a median age at presentation of 24 days (IQR 14–33) meaning that care in a surgical centre would be required for infants below 28 weeks gestation for their first 3–4 weeks of life. This would need significant resource or redistribution of infants and require input from families to determine family perspectives on this. Advances in prenatal and perinatal research (imaging, placental and cord blood pathology, physiological monitoring and serum biomarkers) could potentially better guide identification of those at greatest risk.

Conflicts of interest

The authors declare that they have no competing interests.

References

[1] Stoll BJ, Hansen NI, Bell EF, et al. Trends in care practices, morbidity, and mortality of extremely preterm Neonates, 1993-2012. JAMA, J Am Med Assoc 2015;314:1039—51. https://doi.org/10.1001/jama.2015.10244.

[2] Blakely ML, Tyson JE, Lally KP, et al. Initial laparotomy versus peritoneal drainage in extremely low birthweight infants with surgical necrotizing enterocolitis or isolated intestinal perforation: a multicenter randomized clinical trial. Ann Surg 2021;274:e370—80. https://doi.org/10.1097/SLA.0000000000005099.

[3] Berrington JE, Embleton ND. Discriminating necrotising enterocolitis and focal intestinal perforation. Archives of Disease in Childhood Fetal and Neonatal Edition. Published online; 2021. https://doi.org/10.1136/archdischild-2020-321429. Epub 2021 Jul 13.

[4] Patel RM, Ferguson J, Mcelroy SJ, et al. Defining necrotizing enterocolitis: current difficulties and future opportunities. Pediatr Res 2020;88:10—5. https://doi.org/10.1038/s41390-020-1074-4.

[5] Blakely ML, Tyson JE, Lally KP, et al. Laparotomy versus peritoneal drainage for necrotizing enterocolitis or isolated intestinal perforation in extremely low birth weight infants: outcomes through 18 months adjusted age. Pediatrics 2006;117. https://doi.org/10.1542/PEDS.2005-1273.

[6] Moss RL, Dimmitt RA, Barnhart DC, et al. Laparotomy versus peritoneal drainage for necrotizing enterocolitis and perforation. NEJM 2009;354: 2225—34. https://doi.org/10.1056/NEJMOA054605.

[7] Rees CM, Eaton S, Kiely EM, et al. Peritoneal drainage or laparotomy for neonatal bowel perforation? A randomized controlled trial. Ann Surg 2008;248:44—51. https://doi.org/10.1097/SLA.0B013E318176BF81.

[8] Thakkar HS, Lakhoo K. The surgical management of necrotising enterocolitis (NEC). Early Hum Dev 2016;97:25—8. https://doi.org/10.1016/J.EARLHUMDEV.2016.03.002.

[9] Robinson JR, Rellinger EJ, Hatch LD, et al. Surgical necrotizing enterocolitis. Semin Perinatol 2017;41:70. https://doi.org/10.1053/J.SEMPERI.2016.09.020.

[10] Loh M, Osborn DA, Lui K. Outcome of very premature infants with necrotising enterocolitis cared for in centres with or without on site surgical facilities. Arch Dis Child Fetal Neonatal 2001 Sep;85:F114—8. https://doi.org/10.1136/fn.85.2.f114.

[11] Jones IH, Hall NJ. Contemporary outcomes for infants with necrotizing enterocolitis - a systematic review. J Pediatr 2019:1—7. https://doi.org/10.1016/j.jpeds.2019.11.011. Published online.

[12] Shah J, Singhal N, da Silva O, et al. Intestinal perforation in very preterm neonates: risk factors and outcomes. Journal of Perinatology 2015 2015;35(8): 595—600. https://doi.org/10.1038/jp.2015.41. 35.

[13] Fisher JG, Jones BA, Guttierez IM, et al. Mortality associated with laparotomy-confirmed neonatal spontaneous intestinal perforation: a prospective 5-year multicenter analysis. J Pediatr Surg 2014. Aug;49:1215—9. https://doi.org/10.1016/j.jpedsurg.2013.11.051.

[14] Henry MCW, Moss RL. Neonatal necrotizing enterocolitis. Semin Pediatr Surg 2008;17:98—109. https://doi.org/10.1053/J.SEMPEDSURG.2008.02.005.

[15] Rose AT, Patel RM. A critical analysis of risk factors for NEC. Semin Fetal Neonatal Med 2018;23:374. https://doi.org/10.1016/J.SINY.2018.07.005.

[16] Kelley-Quon LI, Tseng CH, Scott A, et al. Does hospital transfer predict mortality in very low birth weight infants requiring surgery for necrotizing enterocolitis? Surgery 2012;152:337—43. https://doi.org/10.1016/J.SURG.2012.05.036.

[17] Nhs England, Bapm NTG. E08/S/b schedule 2 — the services. service specifications for neonatal intensive care transport 2009.

[18] BRITISH association of perinatal medicine service standards for hospitals august 2010. The British Association of Perinatal Medicine; 2010.

[19] Granger C, Dermyshi E, Roberts E, et al. Necrotising enterocolitis, late-onset sepsis and mortality after routine probiotic introduction in the UK. Arch Dis Child Fetal Neonatal Ed 2022 Jul;107:352—8. https://doi.org/10.1136/archdischild-2021-322252.

[20] Battersby C, Longford N, Costeloe K, et al. Development of a gestational age-specific case definition for neonatal necrotizing enterocolitis. JAMA Pediatr 2017;171:256—63. https://doi.org/10.1001/jamapediatrics.2016.3633.

[21] Kastenberg ZJ, Lee HC, Profit J, et al. Effect of deregionalized care on mortality in very low-birth-weight infants with necrotizing enterocolitis. JAMA Pediatr 2015;169:26—32. https://doi.org/10.1001/JAMAPEDIATRICS.2014.2085.

[22] Jensen EA, Lorch SA. Effects of a birth hospital's neonatal intensive care unit level and annual volume of very low-birth-weight infant deliveries on morbidity and mortality. JAMA Pediatr 2015;169. https://doi.org/10.1001/JAMAPEDIATRICS.2015.1906. e151906-e151906.

[23] Li Y, Shen RL, Ayede AI, et al. Early use of antibiotics is associated with a lower incidence of necrotizing enterocolitis in preterm, very low birth weight infants: the NEOMUNE-NeoNutriNet cohort study. J Pediatr 2020;227: 128—134.e2. https://doi.org/10.1016/J.JPEDS.2020.06.032.

[24] Patel RM, Knezevic A, Shenvi N, et al. Association of red blood cell transfusion, anemia, and necrotizing enterocolitis in very low-birth-weight infants. JAMA 2016;315:889—97. https://doi.org/10.1001/JAMA.2016.1204.

[25] Rabe H, Gyte GML, Díaz-Rossello JL, et al. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. Cochrane Database Syst Rev 2019. https://doi.org/10.1002/14651858.CD003248.PUB4/MEDIA/CDSR/CD003248/IMAGE_N/NCD003248-CMP-003-32.PNG.

[26] Battersby C, Santhalingam T, Costeloe K, et al. Incidence of neonatal necrotising enterocolitis in high-income countries: a systematic review. Arch Dis Child Fetal Neonatal Ed 2018;103:F182—9. https://doi.org/10.1136/archdischild-2017-313880.