Age of onset of necrotising enterocolitis (NEC) and focal intestinal perforation (FIP) in very preterm and low birthweight infants: a systematic review

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ABSTRACT
Objective Review of age of onset of necrotising enterocolitis (NEC) and focal intestinal perforation (FIP) in very preterm and low birthweight infants: a systematic review.

Design Preregistered review undertaken according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses in July 2021 and updated October 2021.

Data sources MEDLINE/ PubMed, Embase, CINAHL and Cochrane Central Register of Controlled Trials.

Eligibility Eligible studies reported age of onset of NEC and/or FIP in randomised controlled trials of >200 or observational studies of >500 infants.

Data extraction and synthesis Titles/abstracts were screened; eligible articles underwent data extraction. Age of onset as day of life (DOL) and/or corrected gestational age (CGA) were extracted alongside study information, such as NEC definition, included population, intervention, location and dates studied. Weighted means were used to compare onset by birth gestation, study type, NEC definition, trial intervention, location and dates studied. Comparison was done by Mann-Whitney U test or one-way analysis of variance.

Results Of the 747 screened studies 188 were eligible. Removal of duplicates, studies without onset data and ineligible populations left 10 RCTs and 14 observational studies contributing 51 NEC cohorts; 49 reported onset DOL and 14 CGA. 2984 cases of NEC had average DOL and 14 CGA. 2984 cases of NEC had average DOL and 14 CGA. 2984 cases of NEC had average DOL and 14 CGA. 2984 cases of NEC had average DOL and 14 CGA. 2984 cases of NEC had average DOL and 14 CGA. 2984 cases of NEC had average DOL and 14 CGA. 2984 cases of NEC had average DOL and 14 CGA. 2984 cases of NEC had average DOL and 14 CGA. 2984 cases of NEC had average DOL and 14 CGA. 2984 cases of NEC had average DOL and 14 CGA. 2984 cases of NEC had average DOL and 14 CGA. 2984 cases of NEC had average DOL and 14 CGA. 2984 cases of NEC had average DOL and 14 CGA. 2984 cases of NEC had average DOL and 14 CGA. 2984 cases of NEC had average DOL and 14 CGA. 2984 cases of NEC had average DOL and 14 CGA. 2984 cases of NEC had average DOL and 14 CGA. 2984 cases of NEC had average DOL 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STRENGTHS AND LIMITATIONS OF THIS STUDY
⇒ This systematic review carried out according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses includes 2984 cases of necrotising enterocolitis (NEC) in very preterm or very low birthweight infants.
⇒ Included studies report a range of mean, median and ‘average’ day of onset of NEC.
⇒ This study explores features including probiotic exposure, feed type, transfusion practices and NICU location expected to impact timing of NEC onset.
⇒ Many large neonatal studies reporting significant numbers of NEC cases do not report time of onset.
⇒ Few studies met our inclusion criteria for focal intestinal perforation cases.

BACKGROUND
Necrotising enterocolitis (NEC) is the most common gastrointestinal medical/surgical emergency occurring in neonates. Focal intestinal perforation (FIP) is an acquired neonatal intestinal disease, defined as a single or occasionally multiple perforations, typically in the terminal ileum and histologically distinct from NEC. There is no gold standard diagnostic test for NEC and while many studies use Bell’s/modified Bell’s criteria to classify cases, miscoding of NEC cases and FIP is well recognised. As a strategy to reduce miscoding some studies/classification systems use time of onset to differentiate NEC and FIP. The data on which this is based are not from exclusively very preterm infants, making the applicability of this data to the exclusively preterm population unclear. We aimed to systematically review published data from randomised trials or observational cohorts reporting NEC or FIP onset in exclusively very preterm or very low birthweight (VLBW) infants.

AIMS
To identify studies reporting NEC or FIP as an outcome, where timing of onset of NEC or FIP was reported. We aimed to describe time of onset data by gestation at birth, NEC definition used and describe differences between ‘early-onset NEC’ and ‘late-onset NEC’, where possible.
MATERIALS AND METHODS

This systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (online supplemental figure 1) and prospectively registered (PROSPERO CRD42021238808).^7^

Search methods for the identification of studies

We searched on MEDLINE/PubMed, Embase, CINAHL and Cochrane Central Register of Controlled Trials. An initial search in July 2021 was updated in October 2021, using terms ‘preterm infant’, ‘very low birthweight’, ‘necrotising enterocolitis’, ‘NEC’, ‘intestinal perforation’ (online supplemental material 1 (Search strategies)). References of included studies were checked for additional studies. We also searched clinical trials registries for ongoing or recently completed trials (https://ClinicalTrials.gov/) and hand searched for trials reported only as abstracts.

Eligibility criteria

Studies were included if written in English, reporting NEC/FIP as outcome and satisfied the following: describing infants ≤32 weeks and/or ≤1500g birth weight, randomised or quasi-RCTs with ≥200 participants or observational studies with ≥500 participants.

Exclusion criteria

Cohorts including only cardiac associated or congenital anomaly-associated NEC were excluded. Studies reporting infants ≥33 weeks gestation or >1500g were excluded unless a cohort meeting eligibility criteria was identified.

Selection of studies

After duplicate removal, two reviewers (ED and CG) screened titles and abstracts for inclusion/exclusion criteria. Potentially eligible articles underwent full-text review (JB, CG, ED). Disagreements were resolved in consensus meetings with all authors.

Risk of bias and quality of evidence assessment

Cochrane Risk-of-Bias Tool was used to assess each randomised controlled trial (RCT).^8^ Quality of observational trials was assessed using the Newcastle-Ottawa Scale.^9^

Data extraction

From eligible studies we collected study characteristics, such as gestation and birth weight eligibility, years of infant recruitment, NEC/FIP definition(s) used, proportion of surgical NEC reported, country, study intervention, total population, average gestation of recruited cohort, cases of NEC reported, average time of onset of NEC/FIP as day of life (DOL) and/or corrected gestational age (CGA) and type of average reported (mean/median) (online supplemental table 1).

Primary outcome

Age at onset expressed as DOL and CGA at onset of NEC and FIP.

Secondary outcomes

Onset of NEC/FIP by gestational week at birth and other study features where reported.

Analysis

Given the large variation in the number of NEC cases reported by studies, we report a narrative description of studies, and weighted average values of time of onset. Comparison between studies used non-parametric tests (Mann-Whitney U test/one-way analysis of variance as appropriate), and linear regression was used to assess correlations between onset and gestation at birth and corrected gestation. A p value of <0.05 was taken as significant.

Patient and public involvement

No patient involved.

RESULTS

Included and excluded studies

After searching and removal of duplicate studies, non-English reports and conference materials 747 studies were screened of which 188 were assessed for eligibility, 125 RCTs and 63 observational. Of these 111 did not contain extractable onset data, 15 were ineligible populations and 3 did not meet prespecified study populations. Citation searching identified 32 studies: 2 duplicates, 9 without onset data, 12 did not meet prespecified criteria and 6 were not in the study population (online supplemental table 1–4, included and excluded studies).

Analysis was undertaken on 10 RCTs and 14 observational studies containing a total of 51 NEC cohorts, 23 randomised and 28 observational cohorts and 2 FIP cohorts.310–32 Details of these studies are in online supplemental table 5.

A mixture of mean, median or unspecified ‘average’ values were given; 49 cohorts reported onset by DOL and 14 by CGA. Where an unspecified estimate of average was given, this was assumed to be the mean.

Quality of studies

Nine of the 10 randomised trials had low risk of allocation bias, 7 had low risk of blinding of participants and personnel, 3 had high risk of bias due to absence of masking measures. Ten of the 14 observational studies scored as good methodological quality, 4 scored moderate (online supplemental tables 6 and 7, online supplemental figure 2).

Primary outcomes

NEC onset by DOL

Twenty-three studies with 49 cohorts reported onset by DOL, ranging from 6 to 30 within observational studies (2615 NEC cases) and 10.7 to 41 for RCTs (369 NEC
cases). Individual numbers of NEC cases in each cohort ranged from 2 to 110 within RCTs and from 4 to 891 in observational studies. Figure 1 shows the relationship between the number of reported NEC cases and the DOL of onset of that cohort ($R^2=0.02$, $p=0.33$).

Figure 2 shows individual DOL onset for each cohort grouped by study design (RCT or observational) alongside weighted average values for RCTs (15.5 DOL), observational (16.9 DOL) and all studies (16.7 DOL).

NEC onset by CGA
Six studies with 14 cohorts reported CGA at NEC onset ranging from 30 to 32 weeks for RCTs (332 NEC cases) and 28.7–31.5 weeks in observational studies (479 NEC cases). Figure 2 shows individual cohort CGA at onset and weighted average values for observational (29.5 weeks CGA), RCTs (30.9 weeks CGA) and all studies (30.1 weeks CGA).

FIP onset
Only two observational studies reported FIP onset data on 633 cases where median DOL onset was 22 and on 38 FIP cases with median onset 6 DOL (IQR: 4–9). Secondary outcomes
Onset of NEC by gestational week at birth of the reported cohort is shown in figure 2. Onset by DOL and average gestation of the cohort did not correlate by linear regression ($R^2=0.025$, $p=0.31$; figure 1) but CGA at onset was correlated to birth gestation of the reported cohort ($R^2=0.41$, $p=0.003$; figure 2).

Anticipated analysis of features of NEC and FIP were only extractable as Bell’s staging, or the proportion of NEC cases that underwent surgery. Five cohorts from three studies reported Bell’s stage 1–3 NEC (DOL onset 20.8 days), all other studies reported only Bell’s stage 2 and 3 (DOL onset 18.5 days) and only two surgical NEC (DOL onset 15.2 days). Twenty-one cohorts from 11 studies reported the percentage of NEC cases that underwent surgery intervention (online supplemental table 5, figure 3). No other anticipated secondary outcomes were extractable.

Further exploration of the impact on NEC onset of clinical and demographic variables included the nature of intervention within trials or observational cohorts (classified as prebiotic, probiotic or symbiotic, blood transfusion or erythropoietin or milk type studies), geographical

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location of the cohort, years in which the study took place and proportion of surgical infants in each cohort (figure 3). None had a statistically significant impact on DOL NEC onset (online supplemental table 8).

DISCUSSION

Quality of data

Quality metrics for included studies were good or moderate although none address the quality of the data relevant to timing of onset, the focus of this review. We noted the non-standardised way that onset data were presented.

Summary and comparison to other literature

We show an average onset of NEC of 16.7 DOL and 30.1 weeks CGA, from 2984 NEC cases ≤32 weeks gestation or ≤1500 g. Individual studies range from 6 to 41 DOL onset and CGA range 28.8–32 weeks. Studies of >100 cases had average onset 12–22.8 days, and the single largest (891 cases) of 15 DOL.22 Contrary to studies between VLBW infants and those >1500 g, we showed no association between birth gestation and DOL onset (R²=0.007, p=0.58). In 1980, Stoll et al reported an association between DOL onset of NEC and gestation at birth in 35 babies.33 They report infants by gestational cohorts that differ from ours with DOL onsets of 20.2 for infants born at ≤30 weeks, and 13.8 for 31–33 weeks. Those with gestation at birth >34 weeks had a mean onset of 5.6 days. González-Rivera also found infants with lower birth gestation had later onset with median DOL onset of 27.5 at <25 weeks gestational age (n=8) and 6 days at 31–32 weeks (n=14), but few infants were included.34 Data published after our search identified an inverse association between birth gestation and DOL NEC onset in 467 infants, between VLBW infants and those >1500 g but not within the VLBW cohort alone.35

Several studies classify NEC categorically by day of onset as ‘early’ or ‘late’ presenting average gestations or birth weights. Teasdale et al (1980) reported early-onset disease had different clinical features from late onset, Wilson et al reported 86 infants <1500 g with early (days 0–10) compared with late-onset (after day 10) NEC,36 contrary to the studies above, early-onset infants had statistically significantly lower GA at birth (28.3 vs 30.2 weeks). In contrast a study of infants <33 weeks found early-onset NEC (<14 days) occurred in more mature and heavier infants than later-onset NEC—median DOL 7 if birth weight >1000 g, 32 if <1000 g. This study also identified peak NEC onset at 32 weeks CGA but did not account for relative proportions of birth gestations.5

We explored five features plausibly impacting DOL NEC onset based on current understanding: NEC definition, intervention, location, proportion of surgical cases and years studied.5,38 None impacted on timing of NEC; however some variable (% of surgical NEC cases, time period and location) groups are arbitrary, and different categorisations may have resulted in different findings. For study interventions it is mechanistically interesting that interventions such as probiotic administration do not appear to impact DOL onset. This is also broadly true within individual studies, where onset in control and exposed cohorts was similar.

NEC definitions

Most studies used Bell’s usually presenting stage 2 and 3, but occasionally stage 1, or surgical NEC, with no statistical difference in DOL onset between definitions.39,40 Bell’s has been criticised for not separating FIP from NEC which then ‘contaminates’ NEC cases impairing research with NEC as an outcome.41 There is agreement that NEC definitions need refinement, if progress in NEC is to advance.42 Recent attempts to do this include the two-out-of-three rule and the Battersby scoring system, no included studies used these newer definitions.

Focal intestinal perforation

Despite sharing some common features with NEC, there are major differences including predisposing factors, radiological findings, prognosis and natural history.1 Older studies are highly likely to be contaminated by FIP unless it has emerged as a new entity recently. We found little data on time of onset of FIP. As survival of the most preterm infants increases and NEC reduction strategies improve, FIP may become proportionately more responsible for stoma formation and associated complications of prematurity, meaning efforts to correctly describe and classify FIP is increasingly important.45

Strengths and weaknesses of the review

We used standardised methodology, protocol registration and reporting according to PRISMA. However, we used total population as eligibility criteria with arbitrary thresholds. In retrospect, given data of interest were focused on NEC, using the number of NEC cases may have been preferable and allowed inclusion of studies that we excluded but which reported more NEC cases than some included here (Dilli et al has only two cases).15 For example González- Rivera et al reported 59 NEC cases but total study population <200 meant exclusion.34 Studies were also excluded because data were only presented graphically and average DOL onset could not be determined.5 We may also have missed relevant non-English articles. Many studies that together report significant numbers of cases of NEC as primary or secondary outcome offer no information at all on timing of onset, including recent large NIHR (National Institute for Health and Care Research)-funded studies.46,47

Traditional meta-analysis of this data was impossible. A variety of means, medians and unspecified ‘averages’ were reported. For analysis we have treated all average values reported as means and presented weighted averages to accommodate large variation in numbers of NEC cases (2–891). Similarly, gestational ages of the study cohorts have been used for analysis of NEC onset, as subgroup data for the NEC cohort alone were rarely or never given.
CONCLUSIONS
Average age at onset of NEC in preterm or VLBW infants with NEC reported in the current literature meeting our inclusion criteria was day 16.7, or at 30.1 weeks CGA. In contrast to current perceptions, we did not find evidence that gestation at birth impacted NEC day of onset within this group. We did not see study interventions that impact on specific aspects of the NEC pathway (eg, transfusion practices/microbiome manipulation by probiotics) impact DOL onset. Importantly many infants were additionally reported as experiencing NEC in well delivered trials, but where reporting of the study did not include these details about NEC.  

Future perspectives
Given its importance to neonatal medicine, standardised reporting for all studies where NEC is a primary or secondary outcome would improve mechanistic and trial understanding. This would include all cases of NEC and FIP, with birth weights and GA at birth of diseased cohorts and whole study cohort, DOL onset as median with IQR and range, proportion undergoing surgery, drainage or dying before laparotomy, and the proportion with histological or postmortem confirmation. Where different gestational cohorts are included, reporting should be by standardised WHO gestational classifications separately—extremely preterm (<28 weeks), very preterm (28–31 weeks), late and moderately preterm (32–36 weeks) and term (≥37 weeks), or individual gestational weeks where possible. This will allow better comparison of NEC cases across studies and identification of associated FIP cases as an indication of possible contamination of a cohort. Including as standard these relatively brief NEC and FIP data items will dramatically improve understanding of one of the most feared complications in neonatal practice.

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