

## Comparative Effectiveness of Prophylactic Therapies for Necrotizing Enterocolitis in Preterm Infants: Protocol for a Network Meta-analysis of Randomized Trials

### Abstract

Necrotizing enterocolitis (NEC) is a common and devastating disease with high morbidity and mortality in premature infants. Current literature on the prevention of NEC has limitations including lack of direct and indirect comparisons of available therapies. We will search MEDLINE, EMBASE, Science Citation Index Expanded, Social Sciences Citation Index, CINAHL, Scopus, ProQuest Dissertations and Theses database, and grey literature sources to identify eligible trials evaluating NEC preventive therapies. Eligible studies will (1) enroll preterm (gestational age <37 weeks) and/or low birth weight (birth weight <2500 g) infants, (2) randomize infants to any preventive intervention or a placebo, or alternative active or nonactive intervention. Our outcomes of interest are severe NEC (stage II or more, based on Bell's criteria), all-cause mortality, NEC-related mortality, late-onset sepsis, duration of hospitalization, weight gain, time to establish full enteral feeds, and treatment-related adverse events. Two reviewers will independently screen trials for eligibility, assess risk of bias, and extract data. All discrepancies will be resolved by discussion. We will specify *a priori* explanations for heterogeneity between studies. For available comparisons between treatment and no treatment, and direct comparisons of treatments, we will conduct conventional meta-analysis using a random effects model. We will conduct a network meta-analysis using a random effects model within the Bayesian framework using Markov chain Monte Carlo methods to assess relative effects of eligible interventions. We will assess the certainty in direct, indirect, and network estimates using the Grading of Recommendations Assessment, Development and Evaluation approach. **Ethics and Dissemination:** We will disseminate our findings through a peer-reviewed publication and conference presentations.

**Keywords:** Multiple treatment comparison, necrotizing enterocolitis, preterm infants, preventive therapies, systematic review

### Introduction

Necrotizing enterocolitis (NEC) is among the most important diseases of the gastrointestinal tract and the most frequent surgical emergency in neonates. The mechanism of NEC is poorly understood but occurs as a result of death of intestinal tissue, which may occur as a result of bacteria in the intestinal tract, or reduced blood delivery. It is characterized by damage to the intestinal tract, which ranges from mucosal damage to full-thickness necrosis and perforation.<sup>[1,2]</sup> The staging system originally described by Bell *et al.*<sup>[3]</sup> categorizes NEC into 3 stages: (1) suggestive, (2) definite, and (3) severe. Stage I NEC presents as feeding intolerance or symptoms of advanced prematurity;

infants with Stage 2 NEC require medical management, and Stage 3 requires surgical intervention.<sup>[4]</sup>

The incidence of NEC, which varies across countries and neonatal centers,<sup>[2]</sup> is estimated to be approximately 3/1000 live births; and it occurs in 1%–5% of neonatal intensive care unit admissions.<sup>[5,6]</sup> NEC is mainly associated with prematurity and low birth weight.<sup>[7]</sup> The incidence of NEC in neonates of very low birth weight (<1500 g) remained unchanged from 1997 to 2007, ranging from 3% to 15%.<sup>[1,8]</sup> According to data from 2009, the incidence of NEC increased, and it is now the 11<sup>th</sup> leading cause of death in infants.<sup>[9]</sup>

Despite advances in neonatal intensive care, morbidity and mortality related to

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NEC have remained unchanged. The NEC associated rate of death is reported to be 20% to 30%, and the rate is higher among infants in need of surgery-up to 50%.<sup>[1,10,11]</sup> NEC is associated with substantial economic burden, with an estimated annual hospitalization cost of more than \$500 million in the United States.<sup>[1]</sup> Infants recovering from NEC are at increased risk for prolonged parenteral nutrition and its related complications, short-bowel syndrome, serious neurodevelopmental delays, and functional disabilities.<sup>[6,7]</sup>

Current recommendations for the management include prompt, early diagnosis, medical management, and surgery if warranted.<sup>[5]</sup> The preferred approach to combat NEC is prophylactic therapy. More than 10 systematic reviews have evaluated various preventive strategies, including maternal and donor breast milk feeding,<sup>[12,13]</sup> prophylactic probiotics,<sup>[14-17]</sup> oral lactoferrin,<sup>[18]</sup> supplementation of formula milk with prebiotic,<sup>[19]</sup> arginine,<sup>[20]</sup> or glutamine,<sup>[21]</sup> and immunoglobulin administration.<sup>[22]</sup>

Nevertheless, considerable gaps in the current literature exist. In particular, most randomized controlled trials (RCTs) compare active treatment to nonactive comparators (e.g., placebo) and there are few direct comparisons among preventive strategies. No systematic review has evaluated all RCT evidence of the leading prophylactic therapies for NEC and no review performed or compared the efficacy and safety of all preventive therapies with one another.<sup>[11-15,18-25]</sup> The only available network meta-analysis assessing the efficacy and safety of food additives (probiotics and prebiotics) for preventing NEC included 25 RCTs,<sup>[26]</sup> whereas the most recent meta-analyses on probiotics included 49 RCTs. No review has used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for evaluating the certainty of prophylactic therapies for NEC. Further, none of the published meta-analyses used emerging methods for handling missing participant outcome data and for assessing risk of bias associated with missing data on risk of bias for NEC prevention.<sup>[27,28]</sup> These limitations highlight the need for a comprehensive review using a systematic approach that compares all available evidence for the prevention of NEC. We aim to conduct a systematic review and network meta-analysis of randomized trials on the effects of preventive therapies in preterm (gestational age <37 weeks) infants on severe NEC, all-cause mortality, NEC-related mortality, and culture-positive sepsis.

## Methods

### Standardized reporting

Our protocol conforms to the preferred reporting items for systematic review and meta-analysis protocols 2015 guideline.<sup>[29]</sup>

### Search strategy

We will systematically search MEDLINE, EMBASE, Science Citation Index Expanded and Social Sciences Citation Index, CINAHL, Scopus, ProQuest Dissertations and Theses database, and Cochrane Central Register of Controlled Trials. Our grey literature search will include trial registries (including ISRCTN registry; [clinicaltrials.gov](http://clinicaltrials.gov); and WHO international RCT registry), BIOSIS Previews, and Google Scholar to find relevant trials. We will not apply language or publication status restrictions. We will work with an experienced medical librarian to develop a search strategy for each database (see appendix 1 for our proposed search strategy for MEDLINE). Reference lists from eligible trials and relevant literature reviews will be scanned for additional trials that may meet our inclusion criteria.

### Eligibility criteria and study selection

Trials will be eligible if they enroll preterm (gestational age <37 weeks) and/or low birth weight (birth weight <2500 g) infants randomized to any of preventive interventions listed below compared to an alternative intervention, placebo, or no intervention. Eligible prophylactic interventions will include maternal or donor breast milk feeding with or without human milk fortifiers, immunoglobulin (IgG or a combination of IgG/IgA) administration, prebiotics (lactoferrin, insulin, galacto- or fructo-oligosaccharides), colostrum, arginine, glutamine, probiotics, and combination of probiotics and prebiotics (synbiotics). Studies published in duplicate or studies that used data from a similar study population in different publications in part or full will be identified and we will extract data from the publication with the most complete dataset (e.g., publications with largest sample size and/or longest duration of follow-up). Appendix 2 presents a draft of the proposed screening tool for determining the eligibility of studies.

Pairs of reviewers, working independently will screen titles and abstracts of identified articles and acquire and

assess the full-text publication for eligibility when one or both reviewers consider a study as potentially eligible. Reviewers will resolve disagreements by consensus and if disagreements are unresolved, discuss discrepancies with a more experienced team member with relevant expertise. We will pilot this step on 10 randomly selected articles (with a ratio of 1:1 eligible and noneligible) and repeat the process until we reach 80% agreement.

### Data abstraction

To help ensure the reliability of independent data extraction, we will begin by piloting our data extraction forms on three randomly selected eligible articles, repeating the process if we find substantial challenges. After our forms have been piloted and standardized, we will conduct calibration exercises between reviewers. To calibrate, we will randomly select four articles that have met our eligibility criteria and each team member will abstract data. Subsequently, team members will meet to resolve the disagreements. We will repeat this process until we reach agreement on 90% of data abstraction items. With accompanying data extraction instructions generated from our piloting and calibration exercises, reviewers, working in pairs, will independently extract all data and resolve discrepancies through discussion. From the included RCTs, the following data will be extracted into a standardized spreadsheet: Study characteristics (the first author, publication year, country of origin, and funding source), participant and trial characteristics (sample size, mean gestational age, birth weight, and corresponding measure of variance (e.g., standard deviation), characteristics of interventions and comparators (time of initiation, doses, species and strains if prebiotics or probiotics used, treatment durations), outcomes of interest (Severe NEC-Stage II or more based on Bell's criteria,<sup>[3,30]</sup> all-cause mortality, NEC related mortality, and late onset sepsis, duration of hospitalization, weight gain, time to establish full enteral feeds, and treatment-related adverse events).

### Risk of bias assessment

Among eligible studies, we will independently assess the following risk of bias issues based on the modified version of the Cochrane risk of bias tool for RCTs: random sequence generation, allocation concealment, blinding study participants (in the case of our study, infants' parents), personnel and outcome assessors, incomplete outcome data, and selective outcome reporting.<sup>[31]</sup> The modified instrument rather than the standard response options (high, low, or unclear risk of bias) will use the following responses: "definitely yes" or "probably yes" (considered as low risk of bias), or "definitely no" or "probably no" (considered as high risk of bias).<sup>[32]</sup> These response options have published evidence of validity for assessing blinding, and will allow our risk of bias assessments to avoid "unclear" as a response option.<sup>[32]</sup> Any discrepancy in assessment of risk of bias will be resolved by discussion, or third party adjudication if needed. We will attempt to contact the authors of eligible

studies for missing information regarding risk of bias assessments and primary/secondary outcomes.

### Data synthesis

For each direct paired comparison, we will calculate relative risk and absolute risk, and the associated 95% confidence intervals (CIs) for dichotomous outcomes. For continuous outcomes, we will analyze the results using weighted mean differences with corresponding 95% CIs. We will employ methods described in Cochrane Handbook both to estimate the mean and SD where median, range, and sample size were reported, and to impute the SD if the SE or SD for the differences are not reported.<sup>[33]</sup> We will use the Q-statistic and  $I^2$  to determine statistical heterogeneity for conventional pair-wise meta-analysis and will look for clinical and/or methodological sources of heterogeneity across included RCTs.<sup>[34]</sup> We will perform subgroup analyses regardless of heterogeneity estimates. We will use the DerSimonian–Laird random-effects model for the meta-analysis of all outcomes.

### Network meta-analysis methods

We will use a random effects model within the Bayesian framework using Markov chain Monte Carlo methods to assess the relative effects of eligible preventive interventions.<sup>[35,36]</sup> However, if we observe any random-effects network estimate inconsistent with its direct estimate, we will report fixed-effects model outputs. We will simulate 100,000 iterations and test the model convergence using the Gelman–Rubin statistic.<sup>[37]</sup> For estimating the precision of the effects, we will use 95% credible intervals through the 2.5 and 97.5 percentiles obtained from the simulations.<sup>[38]</sup>

Although the assumptions for network meta-analysis are similar to conventional meta-analysis, additional key assumptions are transitivity (there are no effect modifiers influencing the indirect comparisons) and coherence (direct and indirect effect estimates being similar).<sup>[39]</sup> We will identify issues of incoherence by comparing direct evidence (i.e., estimates from pair-wise comparisons) with indirect evidence (i.e., estimates from network meta-analysis) using node splitting method.<sup>[34,40]</sup> We will use a Wald test to test any statistical difference between the direct and the indirect estimates.<sup>[41]</sup>

We expect results to differ between studies and we have developed three hypotheses to explain variability: (1) infants with lower birth weight will show smaller treatment effect; (2) infants receiving intervention added to their mother's milk versus donor's milk or formula will show larger treatment effects; and (3) RCTs with higher risk of bias will show larger treatment effects than trials with lower risk of bias.

We will report our findings with probability statements of intervention effects. Probability rankings allow us to

report a chance percentage of which interventions rank higher;<sup>[42]</sup> however, simplifying the results of a network down to probabilities can lead to misinterpretations, specifically, when particular comparisons (i.e., nodes) are not well-connected and/or when certainty in evidence varies between comparisons. Following display of the rank probabilities using rankogram, we will use the surface under the cumulative ranking (SUCRA) to aid in interpretation of relative effect of the interventions; an intervention with a SUCRA value of 100 is certain to be the best, whereas an intervention with 0 is certain to be the worst.<sup>[42]</sup> We will use STATA (StataCorp, Release 14.2, College Station, Texas, USA) and WinBUGS (MRC Biostatistics Unit, Version 1.4, Cambridge, UK) for statistical analyses.

### Assessing certainty in (quality of) the evidence

To assess the certainty in (quality of) estimates of effect across each outcome of interest, we will use the GRADE approach that classifies evidence as high, moderate, low, or very low quality. The starting point for certainty in estimates for randomized trials is high, but may be rated down based on limitations in: risk of bias, imprecision, inconsistency, and indirectness and publication bias.<sup>[43]</sup> The GRADE evidence assessment will be presented in a summary of findings table.

We will also use the GRADE approach to assess the certainty in indirect and network (mixed) effect estimates.<sup>[44]</sup> Indirect effect estimates are calculated from available “loops” of evidence, which includes first-order loops (based on a single common comparator treatment, the difference between the treatment A and B is based on comparisons of A and C as well as B and C) or higher order loops (more than one intervening treatment connecting the two interventions). We will visually examine the network map and where first-order loops are available for indirect comparisons, the certainty of evidence will be the lower of the ratings of certainty for the two direct estimates contributing to the first-order loop (for instance, for the indirect estimate of the effect between A and C through comparisons of A versus C – high quality evidence and B versus C – moderate quality evidence, the certainty will be “moderate” – the lowest of the two direct estimates). In the absence of a first-order loop, a higher order loop will be used to rate certainty in evidence and it will be the lower of the ratings of certainty for the direct estimates contributing to the loop. However, we may rate down the certainty further for intransitivity.<sup>[44]</sup> The transitivity assumption implies similarity of trials in terms of population, intervention, outcomes, settings, and trial methodology.<sup>[38]</sup>

### Discussion

NEC is a devastating gastrointestinal condition among low birth weight neonates and has been one of the most challenging diseases to prevent and eradicate.<sup>[1,2]</sup> Given its relatively high incidence, the high socioeconomic burden,

and scarcity of evidence on the comparative effectiveness of preventive interventions which has likely contributed to variable practice patterns among clinicians, there is a need for a high-quality systematic review and network meta-analysis of the common prophylactic therapies to inform evidence-based prevention of NEC.

There may be limitations to our proposed review methods including the ability to assess risk of publication bias and assess subgroup analysis across diverse interventions using network meta-analysis methods. Our protocol has attempted to document the proposed methods *a priori*, including plans to address the anticipated challenges of such an NMA (e.g., handling missing participant data, assessing subgroup effects and network meta-regression, calculating absolute risk within network of preventive treatments) and assess the certainty in estimates using the GRADE approach.

To ensure that our findings are translated to the neonatology community, we will publish our results in an accessible peer-reviewed journal and present our findings at national and international scientific conferences and on The Hospital for Sick Children and McMaster Children’s Hospital websites.

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### Conflicts of interest

There are no conflicts of interest.

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## Appendix

### Appendix 1: Proposed search strategy for MEDLINE

Database: Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations, Ovid MEDLINE (R) Daily and Ovid MEDLINE (R) <1946 to Present>

#▲	Searches
1	enterocolitis, necrotizing/
2	(necroti?ing enterocolitis or enterocolitis necroticans or nec or typhlitis or pneumatosis intestinalis).tw.
3	1 or 2
4	randomized controlled trial.pt.
5	controlled clinical trial.pt.
6	randomized.ab.
7	placebo.ab.
8	drug therapy.fs.
9	randomly.ab.
10	trial.ab.
11	groups.ab.
12	or/4-11
13	exp animals/not humans.sh.
14	12 not 13
15	3 and 14

### Appendix 2: Draft of proposed screening tool for eligibility of studies

1. Does this study include infants with gestational age <37 weeks or birth weight <2500 g?
  - i. YES
  - ii. NO
  - iii. UNCLEAR.
2. Did the study participants get any NEC preventive intervention?
  - i. YES
  - ii. NO
  - iii. UNCLEAR.
3. The study design is RCT?
  - i. YES
  - ii. NO
  - iii. UNCLEAR.
4. Is there any comparison used for NEC prevention (e.g., usual care or other NEC prevention intervention)?
  - i. YES
  - ii. NO
  - iii. UNCLEAR.
5. Does the study have data for the following outcomes (incidence of Severe NEC, all-cause mortality, NEC-related mortality, and culture-positive sepsis, duration of hospitalization related to NEC, weight gain, duration of parenteral nutrition, time to establish full enteral feeds)?
  - i. YES
  - ii. NO
  - iii. UNCLEAR.