Probiotics for Preventing Neonatal Necrotizing Enterocolitis: A Meta-analysis with Trial Sequential Analysis

Zhang, Y1; Xu, Q2; Zhang, F3; Sun, CL4.

Review question / Objective: The role of probiotics, especially the different types of probiotics in the management of Necrotizing Enterocolitis is still controversial. Thus, we performed a Meta-analysis with Trial Sequential Analysis to determine the efficacy and safety of probiotics for preventing NEC.

Condition being studied: Necrotizing enterocolitis (NEC) is among the most common and devastating diseases in neonates but poorly understood medical condition that is difficult to eradicate encountered in family or general pediatric practice. As the commonest gastrointestinal emergency in neonates, it is categorized into three different stages according to clinical symptoms. The initial typically symptoms include feeding intolerance, increased gastric residuals, abdominal distension and bloody stools and it will deteriorate rapidly to abdominal discoloration with intestinal perforation and peritonitis with or without pneumoperitoneum and systemic hypotension and coagulopathy in which resulted in ischemic necrosis (tissue death) of the intestinal mucosa. As the leading cause of death in preterm infants, the Mortality is as high as 20%-30% and the morbidity, including long term neurodevelopmental impairment, continues to be high after a definite diagnosis of necrotizing enterocolitis, especially in neonates with extremely low birthweight. The development of necrotizing enterocolitis would result in an increased duration of intravenous nutrition in infants, potentially increasing the risk of infectious complications and extend the length of hospitalization. Therefore, early prevention and early diagnosis is particularly crucial.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 31 March 2023 and was last updated on 31 March 2023 (registration number INPLASY202330124).

INTRODUCTION

Review question / Objective: The role of probiotics, especially the different types of probiotics in the management of Necrotizing Enterocolitis is still controversial. Thus, we performed a Meta-analysis with Trial Sequential Analysis to...
determine the efficacy and safety of probiotics for preventing NEC.

**Condition being studied:** Necrotizing enterocolitis (NEC) is among the most common and devastating diseases in neonates but poorly understood medical condition that is difficult to eradicate encountered in family or general pediatric practice. As the commonest gastrointestinal emergency in neonates, it is categorized into three different stages according to clinical symptoms. The initial typically symptoms include feeding intolerance, increased gastric residuals, abdominal distension and bloody stools and it will deteriorate rapidly to abdominal discoloration with intestinal perforation and peritonitis with or without pneumoperitoneum and systemic hypotension and coagulopathy in which resulted in ischemic necrosis (tissue death) of the intestinal mucosa. As the leading cause of death in preterm infants, the Mortality is as high as 20%-30% and the morbidity, including long term neurodevelopmental impairment, continues to be high after a definite diagnosis of necrotizing enterocolitis, especially in neonates with extremely low birthweight. The development of necrotizing enterocolitis would result in an increased duration of intravenous nutrition in infants, potentially increasing the risk of infectious complications and extend the length of hospitalization. Therefore, early prevention and early diagnosis is particularly crucial.

**METHODS**

**Participant or population:** Neonates (including premature and/or low birth weight infant) with gestational age <37 weeks and / or body weight <2500 g) and reporting on any stage necrotizing enterocolitis NEC which are diagnosed by modified Bell staging criteria

**Intervention:** All types of probiotics: multiple strains and different species of probiotics.

**Comparator:** Placebo.

**Study designs to be included:** Randomized clinical trials (RCTs) which investigate the effect of probiotics.

**Eligibility criteria:** Enteral administration of any probiotics started within the first 10 days of life and continued for at least 7 days were eligible. Any types of controls were considered admissible. No restrictions were applied regarding language or dates, nationality, gender and ethnic origin. Nonrandomized or uncontrolled trials were excluded. The literature have no clear definition of NEC and could not extract the data and combined the other drug therapy's literature were also excluded.

**Information sources:** A highly sensitive search in Medline, an analogue search in Embase, and a search in the Cochrane Central Register of Controlled Trials (CENTRAL), WorldCat, TROVE, DART-Europe, and CBM will be performed from their inception to May 2022 by using a combination of MeSH and key word terms. Reference lists of all full-text articles will be hand searched for additional studies. The Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines will be used to lend a reporting framework of this SR.

**Main outcome(s):** ①: Incidence of NEC; ②: Incidence of sepsis; ③: Mortality; ④: Average days of hospitalization.

**Quality assessment / Risk of bias analysis:** The methodological quality of all included RCTs will be evaluated independently by 2 researchers , using the Cochrane risk of bias tool for RCTs. Quality assessment process subsequently will be validated by the third reviewer. Disagreements about whether a study is of low or high quality will be settled through joint discussions. Funnel plots will be used to investigate publication bias. All authors would have access to the study data and review and approve the final manuscript.

**Strategy of data synthesis:** All the data syntheses will be accomplished using
RevMan 5.4 software. We will review the quality of included studies to determine whether differential consideration is merited, and then we will determine the feasibility of completing quantitative syntheses (that is, meta-analyses). Feasibility depended on the volume of relevant literature (we require 3 appropriate studies to consider meta-analysis), conceptual homogeneity of the studies, and completeness of results reporting. When a meta-analysis is appropriate, we will use fixed-effects models or random-effects models to synthesize the available evidence quantitatively. We will hypothesize that the methodological quality of individual studies, the study type, the characteristics of the comparator, and patients' underlying clinical presentation would be associated with the intervention effects. We will plan subgroup to examine these hypotheses.

**Subgroup analysis:** We will conduct subgroup analysis according to different probiotics used.

**Sensitivity analysis:** We will conduct sensitivity analyses to determine whether findings are sensitive to the bias, by restricting the analyses to studies judged to be at low risk of bias for blinded assessment of the primary outcome.

**Language restriction:** No restriction on language.

**Country(ies) involved:** China.

**Keywords:** Necrotizing Enterocolitis; Probiotics; Infant; Systematic review; Meta-analysis; Trial Sequential analysis

**Contributions of each author:**
Author 1 - Yang Zhang.
Email: zhangyang921126@sina.com
Author 2 - Qiong Xu.
Email: 36237063@qq.com
Author 3 - Feng Zhang.
Email: zhangfeng4058@aliyun.com
Author 4 - Chunlei Sun.
Email: sunchunlei1981@126.com