

New Insight into the Use of Prophylactic Probiotic Supplement in Preterm and Very Low Birth Weight Infants

Toby David Lauffer¹, Katherine Lazar¹, Natasha Oh¹, Therese-Mary William^{1,2,*}

¹Kings College London, United Kingdom

²NHS Education South London, United Kingdom

ABSTRACT

Background: Necrotizing enterocolitis (NEC) is the most common serious acquired life-threatening condition, and a major cause of morbidity and mortality in premature and very low birth weight infants. This is primarily due to abnormal gut microbiota and marked dysbiosis in the first few weeks of life of this cohort. Probiotics are live microbial supplement that can support and modulate intestinal microbiome and can potentially reduce NEC rates in preterm and very low birth infants. There is still controversy about the usage of probiotics in preterm and low birth weight infants and which type is more beneficial in reducing NEC. **Aims:** This study was to determine the effect of supplemental triple-species probiotics on reducing the NEC rates in preterm <32 and very low birth weight (<1500g) infants. **Methods:** An ethical approval has been obtained to undertake an observational retrospective qualitative and quantitative study, in two neonatal centres simultaneously introduced triple-species probiotic policy, enrolling preterm <32 weeks and those born 32-36 weeks with very low birth weight <1500g. This was to assess the efficacy of prophylactic triple-species probiotic (Labinic) in reducing NEC and to compare NEC rates before and after probiotic introduction in two eras; Epoch one (1 July 2022 - 20 April 2023) prior to introduction of probiotic and epoch two (21 April 2023 - 25 March 2024) after introduction of probiotic policy. **Results:** Overall, 167 cases met the inclusion criteria from both eras. Table (1) shows NEC rate in epoch one was 17% while NEC rates in epoch two was 3 % only, (p-value $\approx$ 0.0026). The findings show a statistically significant reduction of NEC rate in epoch two. Prophylactic triple-species probiotic supplement has safely achieved 100% success rate in reducing NEC in preterm and very low birth infants without complications. **Conclusion:** Our findings indicate that the prophylactic triple-species probiotic is a reliable and effective cost-effective method to significantly reduce NEC rates in in preterm <32 and very low birth weight (<1500) infants without any adverse complications.

Keywords: Probiotic, Necrotizing Enterocolitis, Preterm, Very Low Birth Infants, Retrospective.

Vol No: 10, Issue: 02

Received Date: July 15, 2025

Published Date: October 23, 2025

*Corresponding Author

Dr. Therese-Mary William

Consultant in Paediatric and Neonates, NHS Education South London, United Kingdom.

Citation: William TM, et al. (2025). New Insight into the Use of Prophylactic Probiotic Supplement in Preterm and Very Low Birth Weight Infants. Mathews J Pediatr. 10(2):41.

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INTRODUCTION

NEC is a costly and the most common potentially life-threatening gastrointestinal acquired condition primarily affecting premature and very low birth weight infants. It also associated with a range of morbidities including short gut syndrome and long-term neurodevelopmental delay [1,2]. The premature and low birth weight infants are at great risk of marked dysbiosis due to imbalance of gut microbiota with lack of beneficial bacteria like Bifidobacteria and high proportion of potentially pathognomonic bacteria like Enterococcus, and Staphylococcus. In contrast, term infants have a more balanced gut microbiome, with a greater abundance of beneficial bacteria [3-5]. Antibiotics commonly used in neonatal centres further reduce the gut microbiome richness and result in overgrowth of resistant pathogenic bacteria [6,7]. The early establishment of a “healthy” gut flora in preterm and very low birth weight infants is essential before the gut gets colonised by pathogenic bacteria, or the existing gut flora gets reduced or destroyed by antibiotic therapy. Probiotics are non-pathogenic and non-toxicogenic live microbial supplement that support and modulate microbiome by successfully colonising the gut with “desirable” bacteria, enhance the gut’s barrier protective function, and reduce the growth of pathogenic bacteria [3-5,8,9]. However, there is still controversy about the usage of probiotics in neonates and which type is more beneficial in reducing NEC [10-16].

AIMS

The aim of this study was to evaluate the benefits of supplemental triple-species probiotics and to determine its efficacy in reducing the NEC rates in preterm <32 and very low birth weight.

METHODS

An ethical approval has been obtained to undertake an observational retrospective qualitative and quantitative study in two neonatal centres that simultaneously introduced triple-species probiotic policy, enrolling preterm <32 weeks and infants born 32-36 weeks with very low birth weight <1500g. The triple-species probiotic Labinic included (lactobacillus Acidophilus Bp-06, Bifidobacterium Infantis Bi-26 and lactobacillus acidophilus NCFM, 0.2ml dose/5 drops = 2 billion bacterial cultures). The Labinic dosage used in these units was 0.1ml twice a day for babies <28 weeks’ gestation and 0.2ml once a day for those $\geq$ 28 weeks’ gestation. The first probiotic dose was administered with first feeds, on day one of life. Probiotics stopped at discharge or at 36 weeks corrected gestational age. Probiotic administration stopped during episodes of NEC or where there is total discontinuation of enteral feeds. Prior to this

study, both neonatal centres simultaneously adopted a standardised enteral feeding guideline for preterm and low birth infants in mid 2021 which was a consistent policy across both epochs. This included mothers’ expressed breast milk (EBM) on day one of life, donor breast milk (DBM) in case of insufficient EBM, Cow’s milk-based fortifier (added to EBM, with full enteral feeds 150 mL/kg/day, stopped before discharge) or preterm formula. Feeds were categorised as exclusive EBM, exclusive DBM, preterm formula, or mixed feeds (combination of EBM, DBM, and formula).

The aim of the study was to assess the beneficial effect of prophylactic triple-species probiotic supplement on reduction of NEC in two eras; Epoch one (1 July 2022 - 20 April 2023) before introduction of probiotic and epoch two (21 April 2023 - 25 March 2024) post introduction of probiotic policy. We excluded preterm infants born outside these neonatal centres, cases where probiotic use was contraindicated due to either severe congenital anomaly, severe illness and when babies did not expect to survive. The primary outcome was NEC (modified Bell’s stage IIA or greater). Sepsis and mortality considered as secondary outcomes.

Data were obtained from electronic patient records (Badger-Net-UK), laboratory results, abdominal X-ray and radiologist reports. Data were independently reviewed by unblinded raters (TL and TMW). Inter-rater agreement of NEC criteria was reached by consensus. Infants treated for either suspected or confirmed NEC, required conservative medical treatment or surgical treatment as per Modified Bell’s criteria (modified Bell’s stage IIA or greater) were considered in this study. Suspected NEC criteria included temperature instability, apnoea, bradycardia, lethargy, increased gastric residual, mild abdomen distension, hemoccult positive stool, radiological evidence of mild ileus, patients treated with triple antibiotic and had bowel rest duration (2-5 days). Confirmed medical NEC criteria included hypotension, metabolic acidosis, thrombocytopenia, neutropenia, abnormal clotting screen, marked abdomen distension/tenderness, abdominal cellulitis, radiological evidence of portal venous gas sign +/- ascites and patients received triple antibiotics and bowel rest duration (5-10 days). Confirmed surgical NEC included all above signs, radiological evidence of bowel perforation, definite ascites, pneumoperitoneum, patients received triple antibiotics and surgical intervention [17].

RESULTS

Overall, 167 cases met the inclusion criteria from both eras, enrolling preterm <32 weeks and infants born 32-36 weeks with very low birth weight <1500g. We excluded preterm infants born outside these two neonatal centres, cases where probiotic use was contraindicated due to either severe

congenital anomaly, severe illness and when babies did not expect to survive. Table (1) shows NEC rate in epoch one was 17% while NEC rates in epoch two was 3 % only (p-value ≈ 0.0026). The proportions of extremely low birthweight infants (<1500g) were similar, and median gestation did not differ in both groups. The reduction of NEC rates after probiotics introduction was independent of variables, including exposure to EBM/DBM and other potential confounding factors such as patent ductus arteriosus and non-steroidal anti-inflammatory drugs (NSAID). The 3% of those developed NEC in epoch two were eligible for receiving probiotic however it was not administrated. NEC

has been confirmed in 18 infants in both eras and required medical conservative treatment only. The mortality rate was 0% in both eras. There was no reported sepsis caused by triple-species probiotic in epoch two. Study findings show a statistically significant reduction of NEC rate in epoch two and that prophylactic probiotic supplement has proven to safely achieve 100% success rate in reducing NEC rate in preterm and very low birth infants. The noticeable improvement in epoch two affected all high-risk preterm and low birth infants irrespective of the gestational age. There was no indication from the available data that probiotic had caused any adverse complications.

Table (1)

Date	Total Number	Probiotic given (%)	Probiotic missed (%)	NEC Rate (%)
Epoch (1)	93	0%	100%	(n=16) 17%
Epoch (2)	74	(n=72) 97%	(n=2) 3%	(n=2) 3 %

DISCUSSION

NEC is a costly and the most common serious acquired life-threatening gastrointestinal condition primarily affecting premature and very low birth weight infants. Although the aetiology for NEC remains poorly understood, it is now increasingly recognised that abnormal gut bacterial colonisation plays a crucial role to the pathogenesis of NEC. Probiotics are Gram positive, non-pathogenic and non-toxicogenic live microorganisms that can confer the gut health of the preterm infants [3-5,8,9]. However, there is still controversy about the usage of probiotics in neonates and which type is more beneficial in reducing NEC [10-16].

NEC is a major cause of morbidity and mortality (approximate mortality of 20-25%) in premature babies. It places huge financial burden on the NHS and on the healthcare system worldwide. Preterm and low birth weight infants have an increased risk of developing NEC in the first few weeks of life due to delayed and abnormal gut microbiota and marked dysbiosis due to the disruption of the normal gut flora development. The gut microbiome has an essential role in the gut maturation, metabolism and digestion of nutrients [1,2]. Preterm infants born with abnormal placental blood flow such as abnormal umbilical artery doppler flow with absent or reversed end diastolic flow velocity, are also at greater risk of developing NEC. This is due to antenatal circulatory changes and increase in mesenteric vascular resistance that leads to reduced intestinal perfusion. This results in

hypoxic ischaemic injury of intestinal mucosa with increased inflammation that further alters gut flora. This circularity changes tend to persist in the postnatal period and increase the risk of developing NEC which is found to be two folds higher in preterm infants with abnormal umbilical artery doppler flow [18-20]. Furthermore, the gut flora can be further compromised and altered by empirical antibiotic that is commonly used in the neonatal intensive care unit which is a contributing factor in the pathogenesis of NEC. Even short course of antibiotics can reduce the gut microbiome richness and result in overgrowth of resistant pathogenic bacteria [6,7]. The key factors of NEC pathogenesis in preterm and low birth weight infants include altered gut microbial system, that potentially dominated with pathogenic bacteria such as *Klebsiella*, *Enterococcus* and *Staphylococcus* and lack of beneficial bacteria such as *Bifidobacterium* which is abundant in the full-term infants' gut [3-5,8,9]. The immaturity of the gut barrier protective mechanism and immune system, along with the exaggerated proinflammatory response to hypoxia and acute ischaemia of the intestine and microbial dysbiosis can progress to necrosis and damage to the entire intestinal wall [18-20]. NEC commonly results in short term complications including peritonitis, sepsis, meningitis, multi-system failure, disseminated intravascular coagulation, cardiovascular shock and potentially death. It also can result in long term complications including intestinal perforation, gastrointestinal strictures, long term parenteral

nutrition, cholestasis, short bowel syndrome, failure to thrive and neurodevelopmental impairment [1,2]. Probiotics are live microbial supplement that support and modulate microbiome development. Moreover, probiotics compete with pathogens and limit its overgrowth by producing antimicrobial compounds, it stimulates proliferation and differentiation of the enterocytes, improve the production of digestive enzymes and enhance preterm gut microbiota. Furthermore, probiotics maintain the integrity of the gut's barrier protective function and reduce the growth of pathogenic bacteria and downregulate the inflammatory process, hence it can reduce the NEC incidence and late onset sepsis in preterm and very low birth infants [3-5,8,9].

CONCLUSION

The probiotic is a reliable, easy, safe and effective method to significantly reduce NEC rates in preterm and very low birth infants. The probiotic supplement modulates the intestinal microbiome and proven to be a key modifier in preventing life threatening NEC and the associated morbidities and mortality. Therefore, it is cost effective in alleviating the financial burden on the NHS and on the health system worldwide.

RECOMMENDATIONS

We highly recommend implementation of routine use of triple-species probiotic for preterm and low birth weight infants for preventing NEC. Further, we suggest expanding the probiotic supplement usage in a wider neonatal population to include other high-risk group at great risk of developing NEC, particularly those born 32-36 weeks and birth weight (1500-1800g) with evidence of antenatal placental insufficiency such as abnormal umbilical artery doppler flow with absent or reversed end diastolic flow velocity and/or received empirical antibiotic for sepsis. Also probiotic can be considered for other babies who are at risk of dysbiosis such as short gut syndrome and gastroschisis. Furthermore, research is required to determine the efficacy of early introduction of probiotic supplement to women during pregnancy to prevent NEC on breast fed infants.

LIMITATIONS

The study sample size was small and based on data collected from two neonatal centres. There is a need for additional large controlled randomised control studies to provide further evidence of the probiotic various strains and combination of probiotics for preventing NEC in wider neonatal population at great risk of developing NEC. There is also need for studies to determine efficacy of early introduction of probiotic supplement to women during pregnancy to prevent NEC on breast fed infants.

ACKNOWLEDGEMENTS

None.

CONFLICTS OF INTEREST AND SOURCE OF FUNDING

None has been declared.

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