East of England Neonatal ODN
(Hosted by Cambridge University Hospitals)

Clinical Guideline: Routine use of probiotics to prevent necrotising enterocolitis in high risk preterm infants.

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For use in: East of England (EoE) Neonatal Units
Guidance specific to the care of neonatal patients.

Used by: Medical Staff, Neonatal Nurse Practitioners, Dietitians, Pharmacists

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Approved by:

Neonatal Clinical Oversight Group	
Clinical Lead Matthew James	**Matthew James**

Ratified by ODN Board:

Date of meeting	

Audit Standards:

- **100% of infants in the EoE meeting the criteria for probiotic administration receive their first dose as soon as they are ready for enteral feeds.**
- **Where an infant, who meets the criteria, does not receive probiotics as soon as they are ready to feed, the reason for deviation is clearly recorded in the medical notes.**

- **100% of parents whose infant meets the criteria for probiotics have the benefits and risks discussed with them and/or receive written information about probiotics.**
- **100% of infants have probiotics discontinued in line with network guidance.**

1.0 Purpose of guideline:

This document is designed to provide guidance for neonatal units within the East of England on the routine administration of multispecies probiotics to all infants who meet the designated criteria listed below.

There is currently insufficient high quality evidence to recommend one probiotic product over the other. Units are therefore recommended to choose one of the combination strain products that has proven effectiveness (table 1) and to develop a local SOP/formulary in conjunction with local microbiology and pharmacy teams based on the evidence and guidance provided within this guideline.

2.0 Background to guideline:

Necrotising enterocolitis (NEC) remains the most commonly acquired gastrointestinal and surgical emergency in preterm very low birth weight (VLBW) infants. It has an approximate mortality of 20-25% and is associated with a range of morbidities that include short gut syndrome, prolonged hospital stay and long term neurodevelopmental delay (1,2).

Although the aetiological basis for NEC remains poorly understood, the bacterial colonisation of an infant's gut is felt to be a significant factor, such that "abnormal" gut bacterial colonisation is now increasingly recognised as central to the pathogenesis of NEC. (3,4)

Whereas healthy, term infants acquire appropriate gut microorganisms soon after birth, (3,4) infection control procedures in the neonatal unit, including antibiotic treatment (5) and reduced exposure to maternal microflora (secondary to delayed parental skin-to-skin contact) all limit the exposure of a preterm infant's bowel to normal commensal microorganisms (3,4,6,7). There is increasing evidence that the resultant altered composition of the microbiota in the preterm infant's bowel may increase their risk of colonisation with pathogenic bacteria, poor immune development and susceptibility to NEC (3,4)

Probiotics are Gram positive, non-pathogenic and non-toxigenic "live microorganisms that, when administered in adequate amounts, confer a health benefit to the host". (8) They have been shown to successfully colonise the gut of preterm infants with "desirable" bacteria and reduce the risk of late onset sepsis (3,9) severe NEC and death.(3,9,10)

An increasing number of randomised controlled trials, systematic reviews and meta-analyses have shown that prophylactic use of probiotics prevents NEC in preterm infants (6,9,11,12,13,14) with the treatment having the greatest effect where multi-strain probiotics were used.

Probiotics have been used in a small number of neonatal units in the EOE for some time, however, the development of a strong evidence base to support mandating probiotic use in all units in the network has, to date, been limited by studies with low power and lack of consistency between probiotic agents, treatment regimens and participant inclusion criteria. This has made direct comparison difficult and the development of network guidance challenging. However the growing body of evidence currently emerging in support of the routine supplementation of all infants (who meet the agreed criteria) with an appropriate probiotic preparation is now further supported by recommendations within the Getting it Right First Time (GIRFT) EOE Action Plan and the GIRFT National Speciality Report for Paediatric General Surgery and Urology (15). These reports recommend the provision of probiotic supplements in all neonatal units and the development of network guidance to support cross network use.

3.0 Who should receive probiotics?

The early establishment of a "healthy" gut flora in preterm infants is essential before either pathogenic bacteria can colonise, or antibiotic therapy can diminish and/or destroy the existing gut flora (2,5). Although some evidence suggests that preterm infants >1000g may benefit more from probiotic treatment than those who are less mature (10,16), there is little evidence to support withholding supplementation from this group. (7) A number of recent RCTs and observational studies (9, 16, 17, 18) have demonstrated a reduction in NEC following routine use of probiotics in infants, including those born <1000g. Indeed a study within the German Neonatal Network demonstrated that the NEC reducing effects of probiotics were even more pronounced in the sub group analysis of preterm infants with birth weights < 100)g. (19) Furthermore in a very recent study that demonstrated a reduction in the incidence of NEC using Labinic over a control, 30%of the infants were <1000g.(20)

Recommendations:

Probiotics are to be offered to those infants at the highest risk of NEC:

- All infants born < 32 weeks gestation.

- All very low birth weight preterm infants (ie 32-37 weeks gestation *and* <1500g.)

- Other babies who are at risk of dysbiosis may benefit from probiotics (eg short gut/gastroschisis). This should be discussed with the infant's parents, neonatologist and surgeon before any decision to supplement is made.

4.0 When should we start and stop probiotics?

Work undertaken in Norwich demonstrated that the administration of probiotics was significantly associated with reduced rates of NEC (9) whereas work undertaken in Newcastle appeared not to show any benefit from routine probiotic supplementation (16). Both studies had similar methodology, however one key difference was the timing of commencement of probiotics. In Norwich supplements were commenced as soon as the infant was eligible for enteral feeds (median day 2), whereas the cohort in Newcastle were commenced on probiotics later in their neonatal journey (median day 6). As early supplementation encourages early colonisation with "desirable" bacteria, and by inference, improves chances of protection, the early introduction of probiotics in the Norwich study could possibly explain the benefits seen in NEC incidence compared to the Newcastle work. This is further reinforced as the apparent impact of reduced NEC incidence with probiotics in the Norwich study was particularly pronounced in the first two weeks of life, thereby implying that achieving early probiotic gut bacterial colonisation is vital (9).

Current data does not allow for a clear recommendation as to the optimal length of probiotic treatment. Best practice would suggest cessation of supplementation around about 34 weeks corrected gestational age as this is deemed the age when NEC risk is reduced. Current network practice for units using liquid probiotics is to continue until the infant's current supply of probiotic is used up once they have reached 32 weeks, thereby minimising waste and potentially conferring ongoing benefit, especially if there is further breastmilk feeding attrition.

4.1 Recommendations for starting probiotics:

- Probiotics are to be started as soon as an infant is deemed ready for enteral feeds (ideally on the first postnatal day).

- If expressed breast milk/colostrum is not available or likely to be delayed then probiotics should still be administered for any infant, either via NG/OG tube or directly into the mouth, once they are deemed ready for enteral feeds (ideally on the first postnatal day)

4.2 Recommendations for stopping probiotics:

- Probiotics should be continued until approximately 34 weeks corrected age for infants born <32 weeks gestation. Consider continuing liquid probiotic preparations until current supply is used up.
- Probiotics should be stopped at discharge for infants <1500g and 32-36 weeks gestation.
- The risks of bacterial translocation and sepsis may be increased when an infant is critically ill (2). Probiotics should therefore be stopped, alongside feeds, if an infant is very unwell, septic or has signs of evolving NEC. They can be recommenced as soon as feeding is re-started.
- Infants transferring between units should continue on probiotic therapy where they still meet the criteria for use. The product used will be dictated by local SOP in line with this network guidance.

5.0 What are the risks of probiotics?

5.1 Probiotic bacteraemia

There is a small risk of sepsis with probiotic bacteria secondary to bacterial translocation from the gut (7), although cases in neonates appear to be rare, associated with low morbidity and are easily treated. The most recent Cochrane review cities no probiotic invasive infections in the >10,000 infants included in the review, (10) although a small number of cases have been reported in the literature. Vigilance and an awareness of the possibility is nevertheless required.

The European society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommend that before commencing probiotic therapy within a neonatal unit, the ability to routinely detect the unit's chosen probiotic strain bacteraemia/fungaemia should be checked with the institution's microbiology department (7) and the most suitable antimicrobial agent be identified for use in the rare instance of probiotic bacteraemia.

5.2 Cross contamination

Data from the PiPS study showed that cross contamination of probiotic treated babies to control (non-treated) babies was common within neonatal units (4). Probiotic bacteraemia can also be caused by cross contamination during preparation of probiotic supplements, especially where powdered products or multi-use drop containers are used (7). Local guidance/SOPs should be developed in order to manage the potential for contamination of surface areas, medications, intravenous catheters and cross colonisation to other infants in the neonatal unit (7).

6.0 Information for parents

The use of probiotics should form part of a unit's standard of care.

The use of probiotics should be discussed directly with parents, preferably antenatally, and supported with an information leaflet (appendix 1). Written parental consent is not required.

A survey of parents of babies on the neonatal intensive care unit confirmed strong parental support for the routine use of probiotics,(ref https://fn.bmj.com/content/99/4/F345.2) However parents have the right to decline the use of probiotic supplementation should they so wish.

7.0 What probiotic preparation should we give?

A strain-specific network meta-analysis published in 2018 (20) identified the probiotic strains which could potentially have the most impact on NEC and mortality in preterm infants. This was followed in 2020 by a position paper from ESPGHAN (7) which conditionally recommends the use of *Lactobacillus GG* or a combination of *Bifidobacterium infantis, Bifidobacterium lactis* and *Streptococcus thermophiles.* There was a neutral recommendation over preparations combining *Lactobacillus acidophilus, Bifidobacterium bifidum and Bifidobacterium infantis.* This position paper however limited its review to randomised controlled trials with >247 infants in the probiotic arm, thereby restricting discussion on a wider range of studies and probiotic strains.

Subgroup analyses undertaken in the most recent Cochrane review showed some evidence of differences in effect sizes depending on the genus of the probiotics used, with larger effects in trials that used combinations of Bifidobacteria and Lactobacilli (with or without Streptococcus thermophilus)(10). Similar findings were identified in a systematic review and network met-analysis undertaken in Canada, where moderate- to high-certainty evidence showed the superiority of combinations of 1 or more *Lactobacillus* species and 1 or more *Bifidobacterium* species over alternative single- and multiple-strain probiotic treatments. (14)

There are three probiotic preparations available in the UK that contain the probiotic strains Bifidobacteria and Lactobacilli (with or without Streptococcus thermophilus). (table 1)

Table 1 Probiotic products available in the UK

Product	Labinic	ProPrems	Infloran
Preparation	liquid	Powder sachets	Powder capsule
Dose	0.2ml od	0.5g od (1 sachet)	250mg od (1capsule) or

			125mg (half capsule) bd
Administration directly onto tongue or Via NGT/OGT	5 drops	Mix with 1-3mL Maternal Expressed Breast Milk (MEBM) or water if MEBM not yet available	Dissolve in 1mL MEBM or water if MEBM not yet available
Bacterial dose (colony forming units)	5 drops (equivalent to approx. 0.2 mL) contains ~2 billion colony forming units of live bacteria in total (*Lactocillus acidophilus* 0.67 $x10^9$, *Bifidobacterium bifidum* 0.67 $x10^9$, and *Bifidobacterium infantis* 0.67 $x10^9$).	0.5g sachet containing ~1 billion bacteria of Bifidobacterium infantis, Streptococcus thermophilus and Bifidobacterium lactis	250 mg capsules contain lyophilised live *Bifidobacterium bifidum* and lyophilised live *Lactobacillus acidophilus* each numbering not $<10^9$ (ie 2 billion live bacteria in total per capsule)
Active probiotic species	• *Lactobacillus acidophilus* • *Bifidobacterium bifidum* *Bifidobacterium Infantis*	• *Bifidobacterium Infantis* • *Bifidobacterium lactis* *Streptococcus thermophilus*	• *Bifidobacterium bifidum* *Lactobacillus Acidophilus*

All three products are manufactured according to Good Manufacturing Practice (GMP) standards, and all have potential advantages and dis-advantages. Units are advised to consider the following points and choose the product that best meets their individual requirements.

7.1 ProPrems

- Powder presentation – highlighted as a cross contamination risk by ESPGHAN (7)
- Store below 25 degrees. Shelf life 2 years post manufacture if sachets kept <25 degrees.

- Contains the three probiotic strains conditionally recommended by ESPGHAN. Recommendation based on RCT data showing clear reduction in NEC over two studies (1244 infants with an average birth weight of approx. 1050g).(7)
- Limited short term use within the EOE network
- Cost – ProPrems is the most expensive of all the products. Current costs (2021) £6.90 per infant per day (£5.52 with discount).
- Manufactured according to the European manufacturing standards (cGMP-certificate of good manufacturing practice) ensuring correct strain identity and lack of contamination.

7.2 Labinic

- Liquid presentation.
- Store at 8-25 degrees. Can be stored at room temperature. Discard bottle once opened for 30 days.
- Neutral recommendation by ESPGHAN.
- A recently published RCT demonstrated that Labinic effectively shortens the time to reach full feeds, reduces the development of feeding intolerances, the number of days with abdominal distention and nil oral, and the incidence of NEC compared to a placebo. (18)
- Recent Cochrane review supports use of Lactobacillus and Bifidobacterium species combinations (10).
- Longterm proven use and experience in EOE Network including published data demonstrating a reduction in NEC associated with routine supplementation. (9)
- Cost – Current cost (2021) £15.95 for a 5ml bottle. Each bottle provides 25 doses (80p per day).
- Manufactured according to the European manufacturing standards (cGMP-certificate of good manufacturing practice) ensuring correct strain identity and lack of contamination.

7.3 Infloran

- Powder presentation – highlighted as a cross contamination risk by ESPGHAN (7)
- Store in fridge, between 2 – 8 degrees.
- No recommendation either way by ESPGHAN
- RCT and observational data show the probiotic strains contained in Infloran to be effective in NEC reduction.(17 19)
- The recent Cochrane review (10) and a systematic reviewand recent meta-analysis of RCTs supports use of Lactobacillus and Bifidobacterium species combinations.(14)
- Lactobacillus acidophilus is a partial D-Lactate producing strain for which there is insufficient safety data available in preterm infants (7)
- Cost - 20 capsules cost £14. (70p per day)

- Manufactured according to the European manufacturing standards (cGMP-certificate of good manufacturing practice) ensuring correct strain identity and lack of contamination.

8.0 Prescription and administration

Probiotics are classified as food supplements in the UK and are not licensed as medicines. The Medicines and Healthcare Regulatory Agency (MRHA) however permit these products to be treated as nutritional supplements for the purposes of prescribing and administration.

In order to ensure appropriate delivery, dosage and governance on the neonatal unit, probiotics should be prescribed via each Trust's agreed pharmacy prescribing system and administered after checking by two registered nurses.

Each unit should devise their own SOP for the handling and administration of their chosen probiotic preparation, with the inclusion of the following:

- Colostrum or EBM should be the liquid of choice when preparing powdered probiotic preparations (ProPrems or Infloran)
- Powdered probiotics should be administered immediately after preparation. Discard any solution not used.
- Where an infant is receiving feeds, give the probiotic dose immediately before a scheduled feed.
- Where an infant is able to receive feeds, but colostrum / EBM is not available continue to administer probiotics. Use sterile water to reconstitute powdered preparations and administer either directly onto the tongue or via NGT/OGT. Flush the tube with 0.5mL sterile water after administration.
- Infants on continuous feeds should receive probiotics, however probiotic preparations should not be added to bottles/reservoirs or syringes of continuous feed.
- Ensure the use of probiotics is recorded in the infant's medical notes and on the infant's daily summary on BadgerNet.

Appendix 1: Example parent information leaflet.

This leaflet provides information for parents about the benefits of giving probiotics to their baby.

What are probiotics?

When a baby is born at term their bowels are full of 'friendly' bacteria which help to keep the bowel healthy. When infants are born prematurely, they do not have the same range or amount of 'friendly' bacteria. This can lead to less 'friendly' bacteria increasing within the bowel, which, in turn, can put them at risk of developing a disease called necrotising enterocolitis (NEC).

NEC is a condition that mainly affects premature infants. It affects the bowels and, when severe, can be life threatening. There are many factors involved in the development of NEC, but we know that the type of bacteria in the bowel is one of them.

Probiotics preparations contain the 'friendly' bacteria normally found in the bowels of babies born at term. They are given to preterm babies to grow in their own bowel and to help stop more 'unfriendly' bacteria from growing out of control.

Research studies have shown that giving probiotics to premature babies can reduce their risk of developing NEC. They may also help prevent other infections and improve overall survival.

In the UK probiotics are classed as food supplements, not medicines. However, the probiotic preparation used in the neonatal intensive care unit (NICU) is produced under the same standards as medicines to ensure its safety and quality.

How are probiotics taken?

Probiotics are given as soon as your baby is ready to feed, at the same time as one of their milk feeds.

How often are probiotics given to my baby?

If your baby is born at less than 32 weeks, probiotics will be given daily until your baby reaches around 34 weeks corrected age, as this is the age the risk of NEC is thought to reduce. However, if your baby is older than this but was started on probiotics because they were very small, the probiotics will stop as part of the discharge planning process. If, for any reason, your baby stops feeds, then the probiotics will stop as well. They will recommence once feeds are restarted.

What are the side effects of probiotics?
Research has shown probiotics to be safe to use in preterm babies. There is however a very small risk that probiotics may cause an infection in some preterm infants. This infection can be treated with antibiotics.
The risk of infection from the use of probiotics is much smaller than the risks associated with the development of NEC. In other words, the benefits of giving probiotics outweigh the risks of not giving them.

Can I refuse to allow my baby to have probiotics?
Yes, you can choose not to allow your baby to receive probiotics, and you can change your mind either way at any time.

Do my baby's milk feeds contain probiotics?
Breastmilk can help to provide some 'friendly' bacteria, and this is one of the reasons why we encourage mothers to try to express breast milk wherever possible.
The benefits of giving probiotics everyday are in addition to the known benefits of breastmilk.
Preterm formulas do not contain probiotics.

What if I have further questions?
If you have any further questions, please ask a member of staff.

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Exceptional Circumstances Form

Form to be completed in the **exceptional** circumstances that the Trust is not able to follow ODN approved guidelines.

Details of person completing the form:	
Title:	Organisation:
First name:	Email contact address:
Surname:	Telephone contact number:
Title of document to be excepted from:	
Rationale why Trust is unable to adhere to the document:	
Signature of speciality Clinical Lead: Date:	Signature of Trust Nursing / Medical Director: Date:
Hard Copy Received by ODN (date and sign):	Date acknowledgement receipt sent out:

Please email form to: mandybaker6@nhs.net requesting receipt.

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