

ORAL PROBIOTICS (*Infloran*® or *LaBiNIC*®) USE FOR PRETERM INFANTS - CLINICAL GUIDELINE

1. Aim/Purpose of guideline

1.1 To provide guidance on the use of probiotics for preterm infants on the Neonatal Unit.

This guidance applies to all staff caring for babies receiving probiotics but is aimed at medical and nursing staff on NICU.

2. Guidance

2.1 Background.

Necrotising Enterocolitis (NEC) is a potentially life-threatening complication of prematurity, with a mortality of 20-25% and significant morbidity (prolonged hospitalisation, short-gut syndrome and impaired neurodevelopment²). Extensive NEC, with full thickness necrosis has a mortality of nearly 100%.

Despite advances in neonatal intensive care over the past 20 years¹, the incidence of NEC in preterm neonates has not changed significantly.²

Although the aetiology of NEC remains uncertain bacterial colonisation of a baby's gut may be a significant factor. Probiotics are gram positive non-pathogenic and non-toxicogenic live microbes which can successfully colonise the gut of preterm infants. Probiotic products such as *Infloran*® contain lactobacilli and bifidobacteria which are the predominant organisms of the GI tract of healthy breastfed infants.³

Probiotics may reduce NEC via multiple mechanisms; they prevent bacterial migration across the mucosa, competitively exclude pathogenic bacteria, and enhance the immune responses of the host.⁴

Potential Benefits

- Decreased risk of death and NEC have been shown in randomised controlled trials, with a 40% reduction in cases of necrotising enterocolitis (stage 2 and 3), with use of *Lactobacillus sporogenes* containing probiotics⁵. This was also consistent with findings from a recent (2014) meta-analysis⁴ which showed a significant reduction for incidence and mortality of NEC. This study⁵ also found a reduction in combined outcomes of death or NEC.
- Improved gastrointestinal function and reduced feed intolerance.
- Though smaller studies have supported the use of *Lactobacillus* containing probiotics, it is important to be aware that initial data from a recently concluded large UK randomised controlled trial (PIPS) evaluating the use of *Bifidobacterium breve* *BBG-001*, showed no significant benefits from using this particular probiotic.⁶

- A meta-analysis of trials⁴, showed probiotic preparations containing either *Lactobacillus* alone or in combination with *Bifidobacterium* to be effective.

Potential Risks.

- Significant side-effects have not been found to be associated with use of probiotics in preterm/low birth weight infants in whom there are no contraindications
- Many level 3 neonatal units worldwide have been using probiotics routinely for over a decade, and have not reported any significant adverse effects².
- Cross-contamination (by stool shedding) can occur, resulting in nosocomial acquisition of probiotic strains by other children in the neonatal unit.²
- There is a lack of significant experience with probiotics, especially in extremely preterm neonates
- Potential problems associated with use of probiotics include Intolerance (higher osmotic load causing abdominal distension, diarrhoea or vomiting), probiotic sepsis and effects of additives such as oligosaccharides (flatulence, loose stools)⁷.
- A recent meta-analysis⁴ reports no trials showing systemic infection with the supplemental probiotics organism.

2.2 Product

“*Infloran*[®]” – 250mg capsules.

Each capsule contains at least 10^9 colony forming units of *Lactobacillus acidophilus* and *Bifidobacterium bifidum*³.

“*LaBiNIC Paediatric Drops*[®]” - 0.38×10^9 colony forming units per drop.

Each dose contains 1.5 billion colony forming units of *Lactobacillus acidophilus*, *Bifidobacterium bifidum (breve)* and *Bifidobacterium infantis*

NB *Infloran*[®] and *LaBiNIC*[®] are not licensed as medicines but are categorised as food products

See APPENDIX 2 for further details.

2.3 Prescription

Infloran[®] should be prescribed as

“125 mg *Infloran* (half capsule)” TWICE DAILY at 08:00 and 20:00 on the drug chart.

“*LaBiNIC*[®]” should be prescribed as

4 drops (0.16 mL) TWICE DAILY at 08:00 and 20:00 on the drug chart

2.4 Indications

All babies < 32 weeks gestation or of birthweight <1500 grams who have commenced enteral feeds. Probiotics should ideally be started on the first day of

feeding (regardless of volume and including trophic feeds), and in general as soon as possible.

2.5 Contraindications

- Babies “nil by mouth”
- Consider temporary discontinuation in any baby who is seriously unwell or septicaemic (including sepsis, NEC and perinatal asphyxia).

2.6 Duration of treatment

- Probiotics can be stopped once the baby is 34 weeks corrected age or after 2 weeks of tolerating enteral feeds with Infloran, whichever is the later.
- In cases where feed intolerance has been an issue, consider continuing probiotics for longer and at least until enteral feeding is well established³.
- Prescription of probiotics should not influence decisions regarding the rate of increase of enteral feeding- this should continue to remain as per the feeding regime being followed, or as directed by the weekly neonatal consultant².

2.7 Obtaining Consent

Take verbal consent from one or both parents/guardian and offer them a Parent Information Leaflet (see appendix 2). Document in the baby’s notes that consent has been given.

References

1. Lin PW, Stoll BJ: Necrotising enterocolitis. *Lancet* 2006, 368:1271-1283.
2. Deshpande GC et al. Evidence-based guidelines for use of probiotics in preterm neonates. *BMC medicine*. 2011;9:92
3. Neonatal GUT flora- prophylactic oral probiotics for prevention of NEC in preterm infants, University Hospitals Bristol NHS foundation trust.
4. AlFaleh K, Anabrees J. Probiotics for prevention of necrotizing enterocolitis in preterm infants. *Cochrane Database of Systematic Reviews* 2014, Issue 4. Art. No.: CD005496. DOI: 10.1002/14651858.CD005496.pub4.
5. F.N. Sari, E.A. Dizdar, S. Oguz, O. Erdeve, N. Uras, U. Dilmen. Oral probiotics: *Lactobacillus sporogenes* for prevention of necrotizing enterocolitis in very low-birth weight infants: a randomized, controlled trial. *Eur J Clin Nutr*, 65 (2011), pp. 434–439
6. Kunz AN, Noel JM, Firchok MP: Two cases of *Lactobacillus* bacteremia during probiotic treatment of short gut syndrome. *J Pediatr Gastroenterol Nutr* 2004, 38:457-458.

7. Lin H-C et al. Oral probiotics prevent necrotising enterocolitis in very low birthweight preterm infants: A multicentre randomised controlled trial *Pediatrics* 2008; 122: 693-700
8. Deshpande et al. Updated meta-analysis of probiotics for preventing NEC in preterm infants. *Pediatrics* 2010; 125(5): 921-30
9. Millar et al. Should the use of probiotics in the preterm be routine *Arch Dis Child Fetal Neonatal* 2012; 97: F70-74
10. Janvier A, Malo J, Barrington KJ. Cohort study of probiotics in a north american neonatal intensive care unit. *The Journal of pediatrics*. 2014;164(5):980-5.
11. Costeloe K. for PiPS group. Early Bifidobacterium breve BBG-001 to prevent necrotising enterocolitis, late-onset sepsis and death: the PiPS trial. *Arch Dis Child* 2014; 99: suppl 2 A23-A24 doi:10.1136/archdischild-2014-307384.75.

APPENDIX 1

Storage and Usage

Infloran[®]

- Store at +2°C to +8°C (i.e. in the normal unit drug fridge.) Use gloves and prepare at a separate time from orally prescribed drugs.
- Prescribe 125 mg Infloran (half capsule) TWICE DAILY at 08:00 and 20:00 on the drug chart
- Start within 48 hours of commencing enteral feeds or as soon as possible.
- Mix one capsule with 2 mL EBM or water and give 1 mL as bolus via NGT. Discard remainder.
- It is safe to provide this extra 1 mL bolus twice daily even in babies only on trophic feeds.
- Consider temporary discontinuation in any baby who is seriously unwell or septicaemic
- Probiotic use should not influence decisions regarding the rate of increase of enteral feeding which remains as per protocol or as directed by the consultant in charge.

LaBiNIC[®]

- Store at room temperature. Use gloves and prepare at a separate time from orally prescribed drugs.
- Prescribe 4 drops (0.16 mL) *LaBiNIC*[®] TWICE DAILY at 08:00 and 20:00 on the drug chart
- Can be given in milk (including via n.g.tube) or given directly into the mouth
- Start within 48 hours of commencing enteral feeds or as soon as possible.
- It is safe to provide this extra volume even in babies only on trophic feeds.
- Consider temporary discontinuation in any baby who is seriously unwell or septicaemic
- Probiotic use should not influence decisions regarding the rate of increase of enteral feeding which remains as per protocol or as directed by the consultant in charge.

APPENDIX 2

Parent/guardian Information leaflet – next page

Probiotics ("Healthy Bacteria") - Information for Parents

Having a premature baby can be difficult and stressful and your views are extremely important to us when we care for your baby. Here we explain some important information about feeding and why we are giving your baby a probiotic (called Infloran or LaBiNIC).

What is different about feeding premature babies?

Premature babies tolerate breast milk best if it is introduced gradually. During that time we may need to use a special intravenous feed called **Total Parenteral Nutrition (TPN)** which contains sufficient protein, energy, vitamins and minerals to make sure your baby receives full nutrition.

Some babies will take longer than others to tolerate full feeding by mouth and while most will remain very well a small number will develop a problem that we call "NEC" (necrotising enterocolitis). Most babies will recover fully from NEC but it can be serious and may require an operation.

What can we do to try to prevent NEC?

Breast milk, even in small amounts, is the best milk for your baby and it also reduces the risks of bowel problems including NEC. We will support you in expressing breast milk but advise you on alternatives if that is not possible.

There is some evidence that giving small amounts of "healthy" bacteria (probiotics - like "Yakult") to preterm babies may reduce the risk of NEC. Studies are still taking place but we now believe there is good scientific evidence to show that they stop some babies getting NEC.

What do we know ?

Probiotics have been studied in over 2000 preterm babies in different countries. Babies who received probiotics developed serious NEC half as

often as those not given probiotics. No serious side-effects have been seen so far but, as with all areas of medicine we adapt practice as further evidence becomes available.

Are there any risks if my baby receives probiotics ?

Probiotics are a food supplement, not a medicine and regulations and standards are the same as for infant formula milks and breast milk fortifiers.

Infection with the probiotic bacteria has not been seen in the babies studied so far but, if it happened, antibiotics are available to kill them.

Are there any risks if my baby does not receive probiotics ?

The biggest risk is the development of NEC but not all cases of NEC will be prevented by probiotics.

What is being offered ?

We think that your baby may benefit from probiotics and will start treatment soon after he or she starts milk unless you tell us not to.

We would normally carry on with the probiotics until baby is about 32-24 weeks corrected age or your baby is discharged or transferred, whichever is sooner.

If you are unsure or would prefer your baby not to have a probiotic or wish to stop treatment then let the nurse caring for your baby know.

Thank you. We hope this information has helped you.

Nursing and Medical Team - Neonatal Unit - RCHT

3. Monitoring compliance and effectiveness

This part must provide information on the processes and methodology for monitoring compliance with, and effectiveness of, the policy using the table below.

Element to be monitored	<i>Development of NEC</i>
Lead	<i>Dr Paul Munyard</i>
Tool	<i>One of the weekly audits</i>
Frequency	<i>Before and after introduction of Guideline. Every three months.</i>
Reporting arrangements	<i>Child Health Audit and Guidelines Committee Meeting</i>
Acting on recommendations and Lead(s)	<i>Child Health Audit and Guidelines Committee</i>
Change in practice and lessons to be shared	

4. Equality and Diversity

4.1. This document complies with the Royal Cornwall Hospitals NHS Trust service Equality and Diversity statement which can be found in the ['Equality, Diversity & Human Rights Policy'](#) or the [Equality and Diversity website](#).

4.2. *Equality Impact Assessment*

The Initial Equality Impact Assessment Screening Form is at Appendix 2.

Appendix 1. Governance Information

Document Title	Use of oral probiotics in preterm infants on the neonatal unit			
Date Issued/Approved:	<i>10 April 2017</i>			
Date Valid From:	<i>10 April 2017</i>			
Date Valid To:	<i>April 2020</i>			
Directorate / Department responsible (author/owner):	<i>Dr Paul Munyard</i>			
Contact details:	<i>01872255081</i>			
Brief summary of contents	Use of probiotics in preterm infants			
Suggested Keywords:	<i>Probiotic. Neonatal.</i>			
Target Audience	RCHT ✓	PCH	CFT	KCCG
Executive Director responsible for Policy:				
Date revised:	10 April 2017			
This document replaces (exact title of previous version):	<i>Use of Probiotics in Preterm neonates</i>			
Approval route (names of committees)/consultation:	<i>Neonatal Guidelines group</i>			
Divisional Manager confirming approval processes	<i>David Smith</i>			
Name and Post Title of additional signatories	<i>Not required</i>			
Signature of Executive Director giving approval	{Original Copy Signed}			
Publication Location (refer to Policy on Policies – Approvals and Ratification):	Internet & Intranet	✓	Intranet Only	
Document Library Folder/Sub Folder	<i>Child Health</i>			
Links to key external standards	<i>None</i>			
Related Documents:	<i>Parent Information Leaflet</i>			
Training Need Identified?	<i>No</i>			

Version Control Table

Date	Version No	Summary of Changes	Changes Made by (Name and Job Title)
<i>February 2015</i>	<i>V1.0</i>	<i>Initial Issue</i>	
<i>April 2017</i>	<i>V2.0</i>	<i>Addition of second preparation of probiotics</i>	<i>Dr Paul Munyard Mr Phil Dale</i>

All or part of this document can be released under the Freedom of Information Act 2000

This document is to be retained for 10 years from the date of expiry.

This document is only valid on the day of printing

Controlled Document

This document has been created following the Royal Cornwall Hospitals NHS Trust Policy on Document Production. It should not be altered in any way without the express permission of the author or their Line Manager.

Appendix 2. Initial Equality Impact Assessment Form

Name of the strategy / policy / proposal / service function to be assessed (hereafter referred to as <i>policy</i>) (Provide brief description):	
Directorate and service area:	Is this a new or existing Policy?
Name of individual completing assessment: Dr P Munyard	Telephone: 01872255081
1. Policy Aim* Who is the strategy / policy / proposal / service function aimed at?	Neonatal Service
2. Policy Objectives*	Inform staff of use of probiotics
3. Policy – intended Outcomes*	To reduced incidence of necrotising enterocolitis and infections
4. *How will you measure the outcome?	Audit above outcomes
5. Who is intended to benefit from the policy?	Neonatal Patients
6a) Is consultation required with the workforce, equality groups, local interest groups etc. around this policy? b) If yes, have these *groups been consulted? C). Please list any groups who have been consulted about this procedure.	No

7. The Impact			
Please complete the following table.			
Are there concerns that the policy could have differential impact on:			
Equality Strands:	Yes	No	Rationale for Assessment / Existing Evidence
Age		No	
Sex (male, female, trans-gender / gender reassignment)		No	

Race / Ethnic communities /groups		No	
Disability - learning disability, physical disability, sensory impairment and mental health problems		No	
Religion / other beliefs		No	
Marriage and civil partnership		No	
Pregnancy and maternity		No	
Sexual Orientation, Bisexual, Gay, heterosexual, Lesbian		No	
<p>You will need to continue to a full Equality Impact Assessment if the following have been highlighted:</p> <ul style="list-style-type: none"> • You have ticked “Yes” in any column above and • No consultation or evidence of there being consultation- this <u>excludes</u> any <i>policies</i> which have been identified as not requiring consultation. or • Major service redesign or development 			
8. Please indicate if a full equality analysis is recommended.			No
9. If you are not recommending a Full Impact assessment please explain why.			
Targeted defined group guideline			
Signature of policy developer / lead manager / director Dr Paul Munyard		Date of completion and submission 10 April 2017	
Names and signatures of members carrying out the Screening Assessment	1. Dr Paul Munyard 2.		

Keep one copy and send a copy to the Human Rights, Equality and Inclusion Lead, c/o Royal Cornwall Hospitals NHS Trust, Human Resources Department, Knowledge Spa, Truro, Cornwall, TR1 3HD

A summary of the results will be published on the Trust’s web site.

Signed _____

Date _____