

Local Guideline



John Hunter
Children's Hospital
CHILDREN, YOUNG PEOPLE AND FAMILIES



Health
Hunter New England
Local Health District

Probiotics in Preterm Infants

Sites where Local Guideline applies

This Local Guideline applies to:

- | | |
|---------------------------------|-----|
| 1. Adults | No |
| 2. Children up to 16 years | No |
| 3. Neonates – less than 29 days | Yes |

Target audience

All clinicians caring for preterm infants in NICU

Description

Probiotic administration guide for preterm infants in NICU

National Standard

Comprehensive Care

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Keywords

Document registration number

Replaces existing document?

Yes

Registration number and dates of superseded documents

JHCH_NICU_09.04

Related Legislation, Australian Standard, NSW Ministry of Health Policy Directive or Guideline, National Safety and Quality Health Service Standard (NSQHSS) and/or other, HNE Health Document, Professional Guideline, Code of Practice or Ethics:

- [Medication Safety in HNE Health PD2013_043:PCP31](#)
- [NSW health Policy Directive PD 2017_013 Infection Control and prevention Policy](#)

Prerequisites (if required)

NIL

Local Guideline note

This document reflects what is currently regarded as safe and appropriate practice. The guideline section does not replace the need for the application of clinical judgment in respect to each individual patient but the procedure/s **require mandatory compliance**. If staff believe that the procedure/s should not apply in a particular clinical situation they must seek advice from their unit manager/delegate and document the variance in the patient's health record.

Position responsible for the Local Guideline and authorised by

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Date authorised

28/05/2019

This document contains advice on therapeutics

Yes

(If Yes) Approval gained from Local Quality Use of Medicines Committee on 09/05/2019

Issue date

28/05/2019

Review date

28/05/2021

Note: Over time links in this document may cease working. Where this occurs please source the document in the PPG Directory at: <http://ppg.hne.health.nsw.gov.au/>

PURPOSE AND RISKS

This local guideline has been developed to provide guidance and information for clinical staff in NICU for probiotic administration in the preterm infant. It ensures that the risks of harm to the infants whilst caring for an infant receiving probiotics are identified and managed.

These risks are minimised by:

1. The preterm infant will receive probiotics to prevent NEC
2. Parents will be fully informed of the advantages of probiotics and receive fact sheet prior to consenting to treatment
3. Probiotics will be stored safely in fridge 2-8°C at all times

Risk Category: Clinical Care & Patient Safety

GLOSSARY

Acronym or Term	Definition
CFU	Colony forming units
ELBW	Extremely low birth weight
NEC	Necrotising Enterocolitis
PROPREMS	Trial for administration of probiotics that confirmed benefits of administration in preterm infants
RCT	Randomised control trial
TGA	Therapeutic Goods Administration
TLR4	Immune system receptor

GUIDELINE

This Guideline does not replace the need for the application of clinical judgment in respect to each individual patient.

Staff Preparation

It is mandatory for staff to follow relevant: "Five moments of hand hygiene", infection control, moving safely/safe manual handling, documentation practices and to use HAIDET for patient/carer communication: **H**and hygiene **A**cknowledge, **I**ntroduce, **D**uration, **E**xplanation, **T**hank you or closing comment.

Guideline for use of probiotics in preterm neonates

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Background:

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Necrotising enterocolitis (NEC) is the commonest and potentially disastrous gastrointestinal surgical emergency in preterm neonates. The incidence of NEC for neonates born at less than 32 weeks gestation in the neonatal intensive care unit at JHCH has been ~2.4% over the past 10 years (~10% for neonates <28 weeks gestation)¹. The mortality related to NEC requiring surgical intervention has been over 50% and is much higher in extremely low birth weight (ELBW, <1000g birth weight) neonates in the JHCH cohort.

The morbidity of definite NEC is significant and includes prolonged hospitalisation, survival with short bowel syndrome, and long term neurodevelopmental impairment, especially in extremely preterm (Gestation < 28 weeks) neonates needing surgery for the illness. Considering the complications and prolonged hospital stay associated with definite NEC,

the economic burden of the illness is also significant²⁻⁴. Preventing NEC is therefore a priority in the support of the very preterm infant.

Benefits of probiotics in preterm neonates:

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The intestine of the normally delivered term, breastfed infant is rapidly colonized with a number of probiotic organisms; in particular Bifidobacteria and Lactobacilli; however, the precise pattern and species involved differ around the world. In contrast, the preterm newborn intestine tends to be colonized by different microorganisms, predominantly coliforms, enterococci, and other bacteroides species, with much inter-individual variation⁵.

Probiotics are “live micro-organisms which when administered in adequate amounts confer a health benefit on the host.” Probiotics may prevent NEC by

- promoting colonisation of the gut with beneficial organisms,
- preventing colonisation by pathogens,
- improving the maturity and function of gut mucosal barrier, and
- by modulating the immune system (e.g. TLR4 receptor, nuclear factor-kB and inflammatory cytokines) to the advantage of the host^{6,7}.

Administration of probiotic organisms as a means of preventing NEC is biologically feasible, is supported by extensive published clinical evidence, and has a clearly beneficial risk-benefit balance. There are now >22 randomized controlled trials (RCTs) of probiotic preparations in preterm infants, enrolling >5500 infants. Systematic reviews of these trials have documented up to 50% reduction in NEC and 30% reduction in all-cause mortality with the routine use of probiotics in high-risk preterm infants⁸⁻¹⁰. Further subgroup analysis of the data from the systematic reviews and from the PROPREAMS trial confirm that these same benefits hold true even in populations with high breast feeding rates and a low baseline incidence of NEC^{8,11}.

Individual experts^{12,13} and the recently updated Cochrane Review⁸ on the subject have commented that based on current evidence, a change in practice favoring routine probiotic supplementation in preterm neonates is justified. Subgroup analyses have reported trends suggesting that a mixture of different organisms may be more effective than a single species⁸.

Selection of probiotic strains

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There are many different mechanisms producing the benefits of probiotics and there are also strain-specific effects. Bifidobacteria and lactobacilli are the species of choice in probiotics, given the evolution of the gut flora in preterm neonates^{14,15}. Bifidobacteria are the dominant strains in infancy, and the combination of lactobacilli and bifidobacteria is known to promote the growth of indigenous lactic-acid bacteria (bifidogenic effect) by formation of short-chain fatty acids as a product of the fermentation process¹⁶.

Evidence indicates that colonisation as well as efficacy from use of a multistrain or multispecies probiotic could be more consistent than that of a monostrain probiotic¹⁷. Experts in the field have recommended that it may be better to avoid untested combinations and reasonable to use probiotic products that have previously been shown

to be effective in RCTs, provided that there has been no change or compromise in the manufacturing technique.

Optimal dose for probiotic supplementation

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An optimal mass or dose is essential for any probiotic strain to survive and colonise the gut. Evidence indicates that to be functional, probiotics have to be viable and in sufficient dosage levels, typically 10^6 to 10^7 colony-forming units (cfu)/g of product¹⁸. Based on the median dose used in the RCTs in preterm neonates it has been suggested that a daily dose of up to 3×10^9 cfu/day may be appropriate and safe for neonates of less than 32 weeks gestation.

Practical issues

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Assurance of good manufacturing practices is important. Probiotics are live microorganisms and are sensitive to oxygen, moisture and heat. Their production and packaging should therefore involve limiting their exposure to oxygen by using barrier packages and eliminating oxygen by flushing with nitrogen. Refrigeration is important to protect the product from significant temperature fluctuations.

Choice of probiotic preparation for NICU, JHCH

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Infloran® (Desma Health Care, Switzerland), 250mg capsules, containing the probiotic bacteria *Lactobacillus Acidophilus* and *Bifidobacterium Bifidum* – 1 billion cfu each, tested in over 400 neonates in RCTs^{9, 10} and meeting all of the above recommendations is one such product currently available in Australia.

Bb M-16V (Morinaga Industries, Japan) available as sachets containing probiotic bacteria *Bifidobacterium breve* up to 5 billion cfu per sachet is another such product. It has been tested for safety¹⁹ and has been shown to be effective in prevention of NEC and mortality in neonates.^{20, 21}

Who is eligible to receive probiotics?

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Gestation up to 31 weeks and 6 days or birth weight < 1500 grams

Exclusion criteria:

1. Major gastrointestinal malformation
2. Contraindications for enteral feeds
3. Life threatening illness/condition

When to start?

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Commence probiotics on day 1. Delaying until commencement of enteral feeds is not necessary. Because of the importance of early establishment of commensal flora in preterm neonates¹⁴, the probiotic supplementation should be started as early as possible before pathogens colonise, or antibiotics destroy the prevailing commensals.

Dose:

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2-3 billion cfu of probiotic bacteria per day, as a single dose, reconstituted with 1-2 mls of breast milk or formula or sterile water (See Appendix 3 and 4)

Storage and Administration of Probiotics:

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The probiotic (Infloran capsules or Bb M-16V sachets) should be stored in the drug fridge (at 2 to 8° C). Probiotics should be administered with routine feeds and should be dissolved in 1-2 ml of milk by the nursing staff looking after the baby at the bedside. The resultant solution should then be administered immediately via a gastric tube. It is recommended to use appropriate PPE as per unit guidelines.

When to stop?

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Temporary withholding of probiotics

- Administration of the probiotic supplementation should be stopped during periods when the enteral feeds are stopped (e.g. severe sepsis, critical illness and NEC) at the discretion of the attending neonatologist. Probiotic supplements should be recommenced 24 hrs after restarting feeds.

Ceasing probiotics

- Probiotics can be ceased at any time the parents wish to withdraw consent for any reason.
- Based on available evidence from RCTs and the inverse relation of gestational age with NEC and all-cause mortality, supplementation should be stopped after reaching the corrected gestational age of 36 weeks (or discharge, **whichever occurs earlier**), when the risk of these adverse outcomes is minimal.
- For infants who are transferred out of the NICU, JHCH, prior to 36 weeks completed gestation, follow the plan below provided the accepting hospital has agreed to continue the probiotic administration.
 - A 2 week supply of probiotics - box to be labelled appropriately with the patient's MRN with appropriate cold chain maintenance (in an esky along with frozen EBM could be appropriate)
 - This should be accompanied with a medication chart with current probiotic prescribed for the appropriate duration, signed by the discharging Neonatologist
 - Also, attach the brief guide on how to administer Infloran® for the nursing staff at the accepting hospital (please see Appendix 3 & 4)

Potential risks of using probiotics:[Top](#)

The administration of live bacteria to immuno-compromised patients such as the very preterm infant cannot be taken lightly. Cases of probiotic-associated bacterial sepsis that have been reported have mostly been secondary to lactobacilli; 4 cases have been reported in young children, and all cases have been mild and easily treated. Most of these cases have involved children with congenital intestinal anomalies. Bifidobacteria has been reported as causing sepsis in a newborn infant; a relatively mild illness occurred in an infant after surgery for omphalocele.

An extensive review of available medical literature has concluded that “Current evidence suggests that the risk of infection with probiotic lactobacilli or bifidobacterium is similar to that of infection with commensal strains, and that consumption of such products presents a negligible risk to consumers, including immuno-compromised hosts”¹⁹. Furthermore, in the large number of published RCTs, now enrolling >5500 preterm infants, no cases of sepsis with probiotic organisms have been reported⁸.

References[Top](#)

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Implementation, Monitoring, Compliance

Approved clinical guideline will be uploaded to the PPG and communication of updated 'Probiotics in Preterm Infants' clinical guideline to NICU staff will be via email and message on the HUB.

Incident investigations associated with this Guideline and Procedure will include a review of process.

The Guideline and Procedure will be amended in line with the recommendations.

The person or leadership team who has approved the Guideline and Procedure is responsible for ensuring timely and effective review of the Guideline and Procedure.

Evaluation will include a review of the most current evidence as well as a consideration of the experience of Neonatal staff at JHCH in the implementation of the Guideline and Procedure.

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APPROVED: NICU Operational Planning and Management 13/02/2019
Clinical Quality & Patient care Committee 28/05/2019

Appendix 1 – Infloran[®] Fact Sheet

FACTSHEET



This fact sheet is for education purposes only. Please consult with your doctor or other health professionals to make sure this information is right for your child. If you would like to provide feedback on this fact sheet, please visit:
<http://hnekidshealth.nsw.gov.au/contacthnekids>

Probiotics

We understand that having a small sick baby in the nursery is not easy. We want to keep you informed about how we plan to care for your baby.

As part of your baby's care, we suggest that your baby should be given probiotics. The probiotic we use is Infloran[®] which is a mix of 2 types of good bacteria. This will help protect your baby and improve feeding.

What is different about feeding babies who are born early?

Most babies, who are born early, need to be fed slowly. Some babies find digesting milk hard, and take longer than others to feed. Most babies remain very well, but a few babies become very sick with a disease called NEC – Necrotising Enterocolitis which affects the gut and can be very serious.

What can we do to try and prevent NEC?

Your choice in how you will feed your baby is important. Breast milk is the best milk for your baby. It reduces the risks of bowel problems. Even small amounts of breast milk are important for your baby. We will support and encourage you if you choose to express breast milk. If you are unable to, or choose not

to express breast milk we will use the best option possible.

What are probiotics?

Probiotics are friendly gut bacteria (like the bacteria found in live yoghurts) that live in our gut and help to keep us healthy. They reduce the growth of harmful bacteria and help in keeping the lining of the gut healthy.

What do we know about probiotics and babies?

Probiotics for prevention of NEC have now been studied in over 5500 babies. These studies show that babies who were given probiotics had 50% less NEC and better survival. Probiotics also helped improve feeding in babies.

How will probiotics be given and for how long?

Infloran[®] powder will be mixed with sterile water or with your baby's milk or formula. It will be given once a day. It will be continued till your baby is 36 weeks corrected age or until your baby is ready to go home.



Are there any risks from not getting probiotics?

From the research done so far we know that babies who do not get probiotics have a higher chance of becoming sick with NEC and dying.

Do you have a choice?

You can choose if your baby gets probiotics or not. If you choose not to give probiotics, your baby will get the same care now and in the future. It will also not affect how you are treated by the staff looking after your baby. You may also change your mind at any time and choose to stop probiotics once they have been started.

Are probiotics licensed for use in babies in Australia?

The probiotic preparation [Infloran](#)® has been listed for use by the Therapeutic Goods Administration (TGA) in Australia.

for your baby. If you have any questions please talk to the nurse or doctor looking after your baby.

For further information on NEC please ask for the NEC factsheet.

References

Deshpande GC, Rao SC, Keil AD, Patole SK. Evidence-based guidelines for use of probiotics in preterm neonates. BMC Med. 2011 Aug 2;9:92

AlFaleh K, Anabrees J. Probiotics for prevention of necrotizing enterocolitis in preterm infants. Cochrane Database of Systematic Reviews 2014, Issue 4. Art. No.: CD005496

Tarnow-Mordi WO, Soll R. Probiotic Supplementation in Preterm Infants: It is time to change practice. J [Pediatr](#) 2014; 164:959-60

Thank you for taking the time to read this information. We hope this will help you in making the right choice

Appendix 2 – Infloran[®]

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Guideline is to accompany infant being transferred out of NICU, JHCH, where the accepting unit have consented to carry on with administering probiotics.

Storage:

Please store the supplied Infloran[®] capsules at 2°C to 8°C.

Dose:

One capsule per day, as a single daily dose

Reconstitution:

Dissolve the contents of 1 capsule of Infloran[®] with 1-2 mL of breast milk or formula or sterile water. This can be done in either a sterile 5 ml syringe or a medicine cup that has been soaking in Milton. **Reconstitute just before administration.**

Administration of Probiotics (Infloran[®]):

- Probiotics should be administered orally or via gastric feeding tube along with routine feeds.
- The reconstituted solution should be administered immediately via a gastric tube. More mature infants who are receiving oral suck feeds may be able to receive the solution via a teat.
- It is recommended to use appropriate PPE as per your unit guidelines.

FEEDBACK

Any feedback on this document should be sent to the Contact Officer listed on the front page.