Kent Surrey and Sussex Neonatal Operational Delivery Network

Use of probiotics for prevention of NEC	
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Implications of race, equality & other diversity duties for this document	This guideline must be implemented fairly and without prejudice whether on the grounds of race, gender, sexual orientation or religion.

Content

Introduction/background

Necrotising enterocolitis (NEC) remains a leading cause of mortality and morbidity in preterm and very low birthweight infants. The aetiology of NEC is multifactorial, which requires a multipronged approach. Every neonatal unit should have clear guidance on enteral feeding, particularly on early introduction of mother's breast milk, colostrum, and use of standardised feeding regime.

Intestinal dysbiosis, the development of an abnormal gut microbiota is an important predisposing risk factor for NEC. Strict antibiotic stewardship for empiric use of antibiotics, total reduction on use of H2 blockers and proton pump inhibitors in preterm infants are helpful interventions. Probiotics, a group of live microorganisms help colonise the gut with friendly microbial flora can help reducing the incidence of NEC.

Aim of Guideline

To provide consistent care for preterm and very low birth weight babies across KSS Network hospitals for use of probiotics in prevention of NEC

Evidence supporting use of probiotics

Recent Cochrane review published in Oct 2020 (1), cautiously interpreted 56 randomised controlled trials with more than 10,000 participants of very preterm (<32 weeks) and very low birth weight (<1500 g) infants that use of probiotics may reduce NEC (RR 0.54, 0.45-0.65, NNTB 33), mortality (RR 0.76, 0.65-0.89, NNTB 50), invasive infection (RR 0.89, 0.82-0.97, NNTB 50). There is no evidence of an effect in the most vulnerable group (babies <28 weeks and weighing <1000g) and also on disability and long term neurodevelopmental outcome.

Multi strain probiotics (Lactobacillus spp+ Bifidobacterium spp) showed a better protection against NEC (RR 0.36, 0.23-0.59, NNTB 26) in 11 trials with 2041 babies, and a combination of (Bifidobacterium spp+ Streptococcal spp) had similar protection (RR 0.36, 0.19-0.68, NNTB 29) in two trials involving 1244 babies (1).

There are comments made about small, heterogeneity of trials, various biases, different probiotic combinations, doses, duration of interventions and target populations in all these trials. (1,2,3). But most importantly, there was no reported incident of probiotic induced invasive blood stream infection in clinical trials- highlighting the safety profile of use of probiotics. A few case reports of Bifidobacterium bacteraemia have been reported in preterm babies receiving probiotic therapy (4,5)

Two other recent network meta-analysis (6,7) have also concluded the multi strain probiotics are better than single strain in lowering rate of NEC (RR 0.47 (0.27-0.79)) and mortality (RR 0.56 (0.34-0.84)). The retrospective study from Norwich (8) also highlighted the positive impact of introduction of multi strain probiotics in reducing the incidence of NEC and also the safety profile of probiotics.

There is evidence to suggest that use of probiotics supplements in VLBW infants fed exclusively human milk is associated with 3-days reduction in the time to achieve full enteral feeds than the

placebo group. Infants exclusively formula-fed did not report any difference between the probiotic and the control group in achieving full enteral feeds (9).

The available multistrain probiotics for neonatal use in UK market is described in Table 1.

Table 1. Types of probiotics available in UK market for neonatal use

Probiotic Product	**Labinic®**	**Infloran®**	**ProPrems®**
Strains	Three strains present in equal quantities • Lactobacillus acidophilus • Bifidobacterium bifidum • Bifidobacterium infantis	• Lactobacillus bifidum • Lactobacillus acidophilus	• Bifidobacterium infantis Bifidobacterium lactis • Streptococcus thermophilus
Dosage form	Oral drops	**Capsules** (opened and contents mixed with sterile water or breast milk)	**Sachet** (Dissolved in 1-3ml of liquid)
Pack size	Multi-dose 5ml bottle	20 capsules	250 Sachets
Strength	0.2ml (5 drops =$2X10^9$ CFU)	250mg ($2X10^9$ CFU)	500mg per sachet ($1X10^9$ CFU)
Cost per pack	£15	£54	£1375
Dosing regimen	5 drops / 0.2ml ONCE daily [4 drops = 0.16ml]	• 250mg (ONE capsule) OD **OR** • 125mg (HALF a capsule) BD Some start at 125mg OD for <1kg till on 40ml/kg/day of enteral feeds (Australia)	ONE (500mg) sachet daily
Total number of doses	25 doses	20 doses	250 doses
Cost per dose	£0.60 per dose	£2.70 per OD dose	£5.50 per dose
Storage	Room temp up to 25° C Can be refrigerated	Fridge: 2 to 8° C	Below 25° C
Expiry once opened	30 days	As stated on pack	As stated on pack
Comments	• Suspended in pharmaceutical grade MCT oil • No allergens (dairy, egg, gluten) • Does not increase	Excipients: lactose, magnesium stearate and skimmed milk	Excipients: Maltodextrin

	osmolality		
Country of origin	South Africa	Italy	Sweden

(Prepared by Sumiah Al-Azieb, Principal Pharmacist, Women and Children Division of Medway NHS Foundation Trust)

(Disclosure: This table gives an account of available multistrain probiotic products in UK. Cost of these products are for guidance only, it may vary from time to time. The guideline group has not suggested or promoted any particular product, and also disclosed no conflict of interest in any of these pharmaceutical products.)

Most of the clinical trials compared the multistrain probiotic products against a placebo. There is no direct comparison between two multistrain products in clinical trials. A Position paper by ESPGHN (2) has highlighted the importance of quality reassurance of the probiotic products, absence of transferable antibiotic resistance genes, and involvement of local microbiologists for monitoring probiotic related sepsis. For multistrain probiotics, the conditional recommendation is the combination of *Bifidobacterium infantis* Bb-02, *Bifidobacterium lactis* Bb-12, and *Streptococcus thermophilus* TH-4 in order to reduce NEC rates.

Indication and duration of treatment

Babies weighing less than 1500 grams and babies born before 32 weeks gestation

Probiotics should be started as soon as possible and preferably with the starting of trophic feeds with colostrum or mother's breast milk. It should be continued till the baby gets to 34 to 36 weeks of gestation or till the time of discharge from the unit. If the treatment has started after 30 weeks, it can be continued till 36 weeks of corrected gestational age. Treatment should be continued in SCU/LNU- when babies are repatriated back to local units from NICU. For convenience, the same multistrain probiotics should be used in the Network.

It is appropriate to withhold the probiotics treatment, if the baby is suspected to have clinical NEC and kept nil by mouth or too unwell with sepsis.

Key practical points:

1. Speak to parents about potential risk and benefit of this therapy / Give Parent Information Leaflet in admission pack as early as possible
2. Probiotics are considered as food products and not licensed as medicinal products.
3. Probiotics has to be prescribed in drug chart.
4. Emphasise to staffs that it is live bacteria, so maintain caution to prevent contamination.
5. Keep the use of the probiotics to preferably once daily dose to minimise multiple handling, It can be used in two divided doses in extreme preterm babies.
6. Put safety plan in place depending on type of product used in the unit.
7. Engage with local Microbiologist about the strain used in the unit.
8. Consider withholding probiotics therapy, if baby is suspected having NEC, quite unwell with sepsis

Auditable standards:

1. Compliance with the guideline for initiation and discontinuation of probiotics therapy in a timely manner
2. Any adverse effects noted during probiotics therapy- invasive bacterial infection with live probiotics micro organisms
3. Incidence of NEC (Bell stage 2 and above) across SEODN before and after introduction of probiotics therapy.

References

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Scope of Guideline Framework

The guideline applies to all Neonatal Units covered by Kent Surrey and Sussex Neonatal ODN. This includes the following hospitals:

Kent, Surrey and Sussex	
Medway Hospital NHSFT	-Medway Maritime Hospital, Gillingham
East Kent Hospitals University NHSFT	- William Harvey Hospital, Ashford -Queen Elizabeth the Queen Mother, Margate
Ashford and St Peter's NHSFT	- St Peter's Hospital, Chertsey
Brighton and Sussex University Hospitals NHST	-Royal Sussex County Hospital, Brighton -Princess Royal Hospital, Haywards Heath
Frimley Health NHSFT	-Frimley Park Hospital
Surrey and Sussex Healthcare NHST	- East Surrey Hospital, Redhill
Maidstone and Tunbridge Wells NHST	- Tunbridge Wells Hospital, Pembury
Dartford and Gravesham NHST	- Darent Valley Hospital, Dartford
Western Sussex Hospitals NHSFT	- Worthing Hospital, Worthing
East Sussex Healthcare NHST	- Conquest Hospital, Hastings
Royal Surrey NHSFT	- Royal Surrey County Hospital, Guildford

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