Probiotics for the Prevention of Necrotizing Enterocolitis in Very Low Birth Weight Infants

Purpose

To implement the routine use of probiotic therapy with initiation of enteral feeding for the prevention of necrotizing enterocolitis (NEC) in low birth weight neonates in all NICUs throughout the Seton Healthcare Network.

Personnel Affected

All licensed nurses, pharmacists, neonatal nurse practitioners, NICU dietitians and physicians working throughout the Seton Healthcare Network who care for NICU patients.

Background

The pathophysiology for necrotizing enterocolitis is multifactorial and includes ischemia, inflammation, immune-mediated response and infection. The most common risk factors noted in the literature are prematurity, low birth weight, and colonization of the gastrointestinal tract with pathogenic bacteria.[4] Gut colonization in the neonate is facilitated by mode of delivery (vaginal versus C-section), the surrounding environment, and dietary factors. Breast milk acts as a first source of bacteria to the neonatal gastrointestinal tract, providing a source of various *Lactobacillus* and *Bifidobacterium* strains that compete with pathogenic bacteria for resources and space within the GI tract. [4,5]

In healthy term infants, gut colonization occurs over the first few weeks of life with the primary resident flora consisting of Lactobacillus and Bifidobacterium species; however, in the preterm infant, this colonization is often delayed due to several factors including exposure to broad spectrum antibiotics, need for medical intervention (intubation, feeding tubes), and delay of breast milk administration.[3] This delay allows for abnormal colonization of the preterm neonatal gut, with the primary bacterial species being Enterococci, Bacteroides, Klebsiella, Clostridium and Staphylococci.[3] This combination of decreased normal bowel flora and increased pathogenic bacteria is one of the factors that place these preterm infants at risk for development of NEC.

Probiotic supplementation in low birth weight, preterm infants has been shown to promote colonization with normal, nonpathogenic gut flora while offering resistance to colonization with pathogenic bacteria.[1] There is also evidence that immunomodulatory effects and promotion of intestinal motor function may occur with administration of probiotics in this patient population. To date, over 25 randomized controlled trials of probiotics in preterm infants have been conducted including over five thousand neonatal patients. Probiotic supplementation in high-risk, preterm infants has been shown to significantly decrease the incidence of NEC, death, and the combined composite outcome of NEC and death without significant adverse effects. [1,15]

Guideline

1. **Inclusion Criteria**

   NICU patients meeting the following criteria and having a physician order should be initiated on probiotic therapy on the day that enteral feedings are initiated (preferably within the first 48 hours of life):

   A. Birth weight ≤ 1500 grams OR gestational age < 32 weeks at birth

   B. In cases of multiple gestation, all infants will be treated as long as at least one infant meets inclusion criteria

2. **Exclusion Criteria**

   A. Any life-threatening congenital anomaly

   B. Major gastrointestinal malformations (gastroschisis, omphalocele, or congenital diaphragmatic hernia)

3. **Suspension of Probiotic Therapy**

   A. Probiotic therapy should be withheld if at any time a patient is made NPO (nothing by mouth) for any reason including suspicion of NEC

   B. For patients who have been made NPO (including post-surgical procedure patients), probiotic therapy should be resumed on the day that enteral feeds are reinitiated

   C. Probiotic therapy should NOT be interrupted or withheld for patients with rule-out, suspected or presumed sepsis or in patients receiving antibiotics for any indication given that the patient has not been made NPOas described above

   - For patients on probiotic therapy requiring blood cultures for sepsis evaluation, both aerobic and anaerobic cultures should be obtained

4. **Dosing of Probiotic Therapy**

   A. Product: Florababy® (Bifidobacterium breve, Bifidobacterium bifidum, Bifidobacterium infantis, Bifidobacterium longum, Lactobacillus rhamnosus)

   B. Dose and dosing regimen: 0.5 grams (2 billion colony forming units [CFU]) once daily

with 2 mL of sterile water

- The first dose should be given on the day that enteral feedings are initiated
- Therapy should be continued until a corrected gestational age of 36 weeks or until discharge, whichever occurs first

5. Physician Orders

A. Physician orders for probiotic therapy may be written as "Probiotics per Protocol"

- When the physician writes "Probiotics per Protocol" an order for the above recommended probiotic dosing and dosing regimen will be entered onto the patient's medication profile by the pharmacist

6. Preparation and Administration

A. Probiotic therapy will be volumetrically dispensed in dry powder form in individually-labeled, sealed, unit-dosed medication cups with lids and delivered to the milk room or other designated location

B. Doses delivered to NICU will be prepared in the milk room and administered via the following procedure by the Charge Nurse, Resource Nurse, or nurse designee on site:

a. Perform hand hygiene, clean the work area with approved disinfectant solution, don clean gloves
b. Tap sealed medication cup lightly to loosen powder
c. Remove cap and tamper resistant seal
d. Draw up 2 mL of sterile water into a syringe and place 2 mL of sterile water into the medication container
e. Secure the cap and shake gently to reconstitute the dry powder
f. Place tip of oral syringe into medication cup, withdraw the entire contents of the medication cup, and cap the syringe using an oral syringe cap (contents will be slightly more than 2 mL)
g. Affix a patient label to each dose to be administered
h. Place all prepared doses in a zip lock bag for transport through the unit
i. Dispose of all medication cups and other preparation supplies, remove gloves, perform hand hygiene, and clean the work area with approved disinfectant solution
j. Promptly administer dose enterally to patient per nursing medication administration policies
k. Perform hand hygiene and change of gloves prior to the administration of each probiotic dose
l. Avoid handling of IV sites, or medications while administering probiotics
m. Dispose of used syringes in the bedside trash can, perform hand hygiene and change of gloves following the administration of each probiotic dose

C. Preferred administration process is for the nurse who mixes the doses (Charge, Resource nurse, or nurse designee on site) to promptly administer dose enterally to the patient per nursing medication administration policies, and while wearing clean gloves. In the case that this

process cannot be followed, for example, increased unit activity that prevents the same individual from mixing and administering the dose, the alternate process is as follows:

- The nurse that mixes the doses will hand off the dose(s) in zip lock bags to one nurse per bay (in units with bays) or to the bedside nurse (in single room units) who will perform hand hygiene and don clean gloves prior to administration of the dose to the patient(s).

Documentation Requirements:

Physician orders, patient administration record (PMAR), Computerized Pharmacy Intervention Program, PharmNet

References

1. AlFaleh K, Anabrees J. Probiotics for prevention of necrotizing enterocolitis in preterm infants. Cochrane Database of Systematic Reviews 2014, Issue 4. Art. No.: CD005496
2. Al-Hosni M, Duenas M, Hawk M, Stewart LA, Borghese RA, Cahoon M, et al. Probiotics-supplemented feeding in extremely low-birth-weight infants. Journal of Perinatology 2012;32(4):253–9.
3. Bin-Nun A, Bromiker R, Wilschanski M, Kaplan M, Rudensky B, Caplan M, et al. Oral probiotics prevent necrotizing enterocolitis in very low birth weight neonates. Journal of Pediatrics 2005;147(2), 192-6.
4. Braga TD, da Silva GA, de Lira PI, de Carvalho Lima M. Efficacy of Bifidobacterium breve and Lactobacillus casei oral supplementation on necrotizing enterocolitis in very-low-birth-weight preterm infants: a double-blind, randomized, controlled trial. The American Journal of Clinical Nutrition 2011;93(1):81–6.
5. Dani C, Biadaioli R, Bertini G, Martelli E, Rubaltelli FF. Probiotics feeding in prevention of urinary tract infection, bacterial sepsis and necrotizing enterocolitis in preterm infants. A prospective double-blind study. Biology of the Neonate 2002;82(2):103-8.
6. Fernández-Carrocera LA, Solis-Herrera A, Cabanillas-Ayón M, Gallardo-Sarmiento RB, García-Pérez CS, Montaño-Rodríguez R, et al. Double-blind, randomised clinical assay to evaluate the efficacy of probiotics in preterm newborns weighing less than 1500 g in the prevention of necrotising enterocolitis. Archives of Diseases in Childhood. Fetal and Neonatal Edition 2013;98(1):F5-9.
7. Janvier A, Malo J, Barrington K. Cohort Study of Probiotics in a North American Neonatal Intensive Care Unit. Journal of Pediatrics 2014;164(5):980-985.
8. Kane AF, B AD, Denning PW, Shane AL, Patel RM. Routine Supplementation of Lactobacillus rhamnosus GG and Risk of Necrotizing Enterocolitis in Very Low Birth Weight Infants. The Journal of Pediatrics 2018;195:73-79.e2.
9. Kitajima H, Sumida Y, Tanaka R, Yuki N, Takayama H, Fujimura M. Early administration of Bifidobacterium breve to preterm infants: randomised controlled trial. Archives of Disease in Childhood. Fetal and Neonatal Edition 1997;76(2):F101-7.
10. Li Y, Shimizu T, Hosaka A, Kaneko N, Ohtsuka Y, Yamashiro Y. Effects of bifidobacterium breve supplementation on intestinal flora of low birth weight infants. Pediatrics International 2004;46(5):509-15.
11. Lin HC, Su BH, Chen AC, Lin TW, Tsai CH, Yeh TF, et al. Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. Pediatrics 2005;115(1):1-4.
12. Lin HC, Hsu CH, Chen HL, Chung MY, Hsu JF, Lien RI, et al. Oral probiotics prevent necrotizing enterocolitis in very low birth weight preterm infants: a multicenter, randomized, controlled trial. Pediatrics 2008;122(4):693–700.
13. Manzoni P, Mostert M, Leonessa ML, Priolo C, Farina D, Monetti C, et al. Oral supplementation with Lactobacillus casei subspecies rhamnosus prevents enteric colonization by Candida species in preterm neonates: a randomized study. Clinical Infectious Diseases 2006;42(12):1735-42.

14. Manzoni P, Rinaldi M, Cattani S, Pugni L, Romeo MG, Messner H, et al. Bovine lactoferrin supplementation for prevention of late-onset sepsis in very low-birth-weight neonates: a randomized trial. JAMA 2009;302(13):1421-8. [DOI: 10.1001/jama.2009.1403]
15. Mihatsch WA, Vossbeck S, Eikmanns B, Hoegel J, Pohlandt F. Effect of Bifidobacterium lactis on the incidence of nosocomial infections in very-low-birth- weight infants: a randomized controlled trial. Neonatology 2010;98(2):156–63.
16. Millar MR, Bacon C, Smith SL, Walker V, Hall MA. Enteral feeding of premature infants with Lactobacillus GG. Archives of Disease in Childhood 1993;69(5 Spec No):483-7.
17. Patel RM, Underwood MA. Probiotics and necrotizing enterocolitis. Seminars in Pediatric Surgery 2018;27(1):39-46.
18. Samanta M, Sarkar M, Ghosh P, Ghosh JK, Sinha MK, Chatterjee S. Prophylactic probiotics for prevention of necrotizing enterocolitis in very low birth weight newborns. Journal of Tropical Pediatrics 2009;55(2):128-31.
19. Sekhon MK, Grubb PH, Newman M, Yoder BA. Implementation of a probiotic protocol to reduce rates of necrotizing enterocolitis. Journal of Perinatology 2019;39:1315-1322.
20. Singh B, Shah PS, Afifi J, Simpson CD, Mitra S, Dow K, El-Naggar W. Probiotics for preterm infants: A National Retrospective Cohort Study. Journal of Perinatology 2019;39:533-539.

EBOC Project Owner: Dr. Molly Pont

Revision History

Approved: 12/2014
Reviewed: 02/2020

Neonatology EBOC Team:

Lyndrick Hamilton, PharmD
Molly Pont, MD
Neonatal Nutrition Committee