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Controversies and Unresolved Issues





Probiotics and Prebiotics

[*Read FDA's 2023 Probiotics Warning](#)

Background, Rationale, and Goals

Probiotics are live microbes that beneficially affect the health of the host.¹⁻³

- The establishment of a healthy gut microbiome is essential for lifelong health and well-being but the preterm infant is predisposed to gut dysbiosis, an abnormal flora that may predispose to disease or poor health.⁴
- In the preterm infant gut, there are delays in bacterial colonization, reduction in total number of bacteria and reduced diversity of the microbial community.
- These effects may be attributed to the lack of contact with normal maternal flora, early antibiotic exposure, and limited use of human milk, especially for the initiation of feedings.
- Dysbiotic changes in the gut flora with Gammaproteobacteria before infants develop NEC have been described.⁵⁻⁷
- Numerous single center and multicenter studies (preterm infants total >10,000) have evaluated the effectiveness of multiple probiotic regimens for NEC prevention, mortality and other morbidities.⁸⁻¹⁰
- Systematic reviews have strongly suggested that probiotics reduce the incidence of NEC and may affect all-cause mortality but there are minimal effects seen in the smallest preterm infants with birth weight less than 1000 grams.¹¹

Prebiotics are non-living substances that beneficially affect the host by selectively stimulating the growth and activity of certain bacteria in the colon that improve the health of the host.^{3,12,13}

- Human milk contains over 150 different prebiotics primarily in the form of oligosaccharides that are small sugar chains, typically 3 to 7

monosaccharides in length.¹⁴

- These substances are naturally present in breastmilk, are not degraded by gastric acid, and support the growth of probiotics species in the GI tract.¹⁵
- Specific oligosaccharide structures may confer protection against NEC.¹⁶
- Supplementing formula milk with a mixture of galacto- and fructo-oligosaccharides not typically found in human milk stimulates intestinal growth of bifidobacteria similar to those found in preterm infants fed human milk.¹⁷
- Recent formulas can contain oligosaccharides found in human milk such as 2'FL and may help reduce respiratory morbidities in infants.¹⁸
- Prebiotic related health benefits in preterm infants have not yet been demonstrated. While term formulas contain probiotics and/or prebiotics, current preterm formulas do not contain either. Continuing research needs to be done on the effects of prebiotics on intestinal flora, feeding tolerance and the risk of NEC in preterm infants.

Recommendations, Guidelines and Algorithms

- Providing a diet based on human milk is the single most powerful method to positively influence the infant gut microbiome as human milk contains a potent mixture of natural prebiotic oligosaccharides and probiotics.
- While there is mounting evidence to support the use of exogenous probiotic treatment for the prevention of NEC, the type and quality of probiotics, dose, duration and safety measures in the NICU have not been well established yet.
- There are no FDA approved probiotics at present. The regulatory environment for probiotics is

complex and may limit the type of probiotics available for clinical use in the prevention of NEC in preterm infants.

- Although term formulas now contain some plant and human based oligosaccharides, clinical trials with prebiotics in preterm infants are required before establishing any recommendations for this promising group of compounds.

Quality & Process Improvement

- Establish guidelines for human milk use recognizing the differences in probiotic/prebiotics in mother's milk versus donor milk and other forms of processed human milk.

Outcome/Process Measures

- Human milk initiation day of life
- Human milk dose over hospital stay
- Human milk use at discharge
- All human milk at discharge

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Pacifiers in the NICU

Background, Rationale, and Goals

- Despite earlier evidence that pacifier use was detrimental to exclusivity and duration of breastfeeding in term infants,^{19,20} a recent Cochrane Review²¹ reported no significant effect on prevalence of breastfeeding or exclusive breastfeeding up to 4 months. The updated WHO/UNICEF 2017 Baby-Friendly Hospital Initiative guidelines has removed pacifier restriction from its key clinical practices.²² Because of the low quality of the available evidence used by the WHO/UNICEF to adjust Step 9 (no pacifiers or artificial teats) and the desirability of newborns to stimulate a mother's milk supply by suckling at breast frequently rather than a pacifier, the United States Baby-Friendly accreditation organization (www.babyfriendlyusa.org) has not changed their recommendations.
- In preterm infants, non-nutritive sucking (NNS) has been associated with decreased hospital stay and faster transition from gavage to bottle feeding.²³ There is controversy about whether the use of pacifiers while gavage feeding is associated with more rapid gastric emptying and more rapid weight gain.²⁴
- Recent studies have not demonstrated any detrimental effect on short or long term breastfeeding rates in preterm infants.²⁵ Indeed, a preliminary study of a motorized "pulsating" pacifier seemed to accelerate the development of NNS and facilitate improved oral intake.²⁶

Recommendations, Guidelines and Algorithms

- When the mother is absent, a pacifier may be beneficial for soothing, when other techniques are not available or are ineffective.
- Pacifiers should not be used to delay feedings, even in anticipation of the mother's arrival. Crying in a term infant is a late sign of hunger.²⁷ A fretful

infant expends calories better reserved for growth, and an exhausted infant is less capable of feeding at the breast.

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Cytomegalovirus Transmission to Preterm Infants During Lactation

Background, Rationale, and Goals

- Maternal CMV reactivation of most seropositive mothers during lactation with shedding of viral DNA and viro lactia can be detected already in colostrum by 3 days and normally ends at about 3 months after birth.
- CMV in milk is a local process without detection in plasma, throat or cervical swabs.
- Full-term infants have not been shown to have any sequelae from CMV transmission via breastmilk.
- The main risk factors for symptomatic disease are extremely low birthweight, early transmission, low gestational age, and low infant IgG titers.
- The exact milk to infant transmission rate varies from study to study.
- Despite transmission, actual illness (sepsis-like presentation) appears rare.
- There are now some data supporting the (rare) possibility of cognitive consequences of postnatally acquired CMV in preterm infants, but most studies show no differences in preterm infants with and without postnatally-acquired CMV infection.²
- Freezing at -20°C for various time intervals from 18 hrs to 10 days decreases the risk of CMV transmission but does not eliminate it.
- Holter pasteurization or heating to 62 °C for 5 seconds eliminates viral transmission.
- Microwave radiation or ultraviolet-C-irradiation may eliminate CMV but their efficacy and potential harmful effects on breastmilk factors are not known at present.

For a full review of the current literature refer to Hamprecht K and Goeltz R. "[Postnatal Cytomegalovirus Infection Through Human Milk in Preterm Infants: Transmission, Clinical Presentation, and Prevention](#)" in *Clinics in Perinatology*, March 2017; 44(1):121-130.¹

Recommendations, Guidelines and Algorithms

General:

- The use of human milk for NICU infants should be continued.
- Established practice and guidelines for the prevention of CMV via blood products should continue.
- Breastfeeding or providing mother's breastmilk for full-term infants and preterm infants with CMV seronegative mothers should continue without further laboratory investigation.
- The low risk of symptomatic CMV infection in the extremely premature infant of a CMV-positive mother should be discussed with the mother and balanced against the known risks associated with lack of breastmilk use.
- The current frequency and nature of postnatal CMV infections in each neonatal unit should be tracked.
- CMV policies should be updated as new data become available.

Clinical:

- The mother's blood (CMV IgG) of all VLBW infants (< 1500 g or < 32 wks) admitted to the NICU may be screened for CMV serostatus. Maternal screening may be done on the high risk perinatal unit prior to delivery if possible.
- Appropriately pasteurized or HTST heat-treated donor human milk products may be used at any time without risk of CMV transmission.
- Fresh, refrigerated or frozen donor milk should not be used for VLBW infants unless the donor is CMV negative.
- Short-term heat inactivation for 5 seconds at 62° C (144° F) maintains the benefits of feeding human

milk while removing CMV transmission but this is not clinically available.

- Given the peak time of virolactia (and therefore transmission) appears to be 3-4 weeks postpartum, colostrum (the first 3-4 days of colostrum) may be used fresh or frozen.
- If the mother is CMV seropositive, freeze all maternal breastmilk for at least 24 hrs prior to feeding until the infant is > 32 weeks corrected age or feeding directly at the breast.
- Infants greater than 3 weeks of age with signs and symptoms consistent with CMV (respiratory deterioration, hepatitis, leucopenia, thrombocytopenia) or a sepsis-like syndrome should be evaluated for CMV:
 - Quantitative plasma PCR for CMV
 - Urine culture for CMV
 - Review admission maternal CMV status and initial infant status if mother was CMV positive.

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