Beneficial Effect of Breast Milk in the Neonatal Intensive Care Unit on Development and Outcomes of Preterm Infants

Sanjay Kumar Azad.

Abstract: Infant born preterm are at high risk of mortality and are some of the most expensive patients in the hospital. Preterm infants are susceptible to prematurity related morbidities including late onset sepsis, necrotizing enterocolitis, retinopathy of prematurity, cognitive development, immunity improvement. The incremental cost of these morbidities during the neonatal intensive care unit and frequently re-hospitalization is high of cost effect. Breastfeeding has show to reduce both the incidence and severity of must of these morbidities and has direct impact on the cost of neonatal intensive care unit hospitalization with development of the preterm infant. This review describes the outcome of beneficial effects of breastfeeding in preterm who are admitted in neonatal intensive care unit.

Keywords: Breastfeeding, Preterm infant, NICU, Outcome.

Address Tongji University, Shanghai First Maternity And Infant Hospital.
(Affiliated to Tongji University) Department of Neonatology, Shanghai 1st Maternity and Infant Hospital, TongJi University School of Medicine, Shanghai 200040, P. R. China.E-mail:sanjayazad43@yahoo.com
Correspondence to: Professor, Dr. Xiao-Ming Ben, Department of Neonatology, Shanghai 1st Maternity and Infant Hospital, TongJi University School of Medicine, Shanghai 200040, P. R. China:e.mail; xben130@yahoo.com

Introduction

There are several short and long term beneficial effect of breastfeeding in preterm infants. Breastfeeding helps in the development of the preterm infant's immature host defense. The implication for a reduction in incidence of NEC include not only lower mortality rates but also lower long term growth failure and neurodevelopmental disabilities. Clinical feeding tolerance is improved and the attainment of full enteral feeding is hastened by a diet of human milk.
Neurodevelopmental outcome is improved by feeding of human breast milk, psychological and relation aspect is created in between mother and infant.
Some studies shows that the intelligence test results and white matter and total brain volume are greater in infants who had received human milk as infant in NICU. Preterm receiving the breastfeeding in NICU has significantly greater scores for mental, motor and behavior in the later age. Breastfeeding in preterm infants in the NICU also is associated with lower rates of severe retinopathy of prematurity. Preterm infants with breastfeeding is also associated with lower rates of metabolic syndrome, and in adolescents, it is associated with lower blood pressures andlow-density lipoprotein concentrations and improved leptin and insulin metabolism.It also reduces the risk of chronic lung disease. It reduces the chance of being rehospitalization after NICU discharge.[1]

Infants considered mild or moderately preterm (32 0/7-36 6/7 weeks gestation) and "late preterm" (unconventially defined as 33 0/7-36 6/7 weeks gestation), preterm infants who are breastfed tend to be re-admitted to the hospital with diagnoses of failure to thrive, jaundice, and dehydration more frequently than those who are not breastfed, a finding largely attributed to insufficient breast milk intake. Breastfeeding duration statistics for late preterm infants are difficult to compile among studies due to wide variations in measurement periods (e.g., days, weeks, months), type of breastfeeding examined (e.g., exclusive versus any), regional differences (e.g., rates higher in some countries, such as Australia), and inconsistencies in gestational week classification categories (e.g., infants of 30 0/7-35 6/7 weeks often grouped as "moderately preterm"; "late preterm" or "near-term" may include gestational weeks 34-<40). However, as study data demonstrate in Table 2, with the exception of one study breastfeeding tends to decrease over the postpartum period within the late preterm population, and rates may even be less than that for either term or earlier preterm infants at

several weeks postpartum suggest that their finding of higher breastfeeding rates among early preterm infants (< 32 weeks) may be a result of extra vigilance, breastfeeding support, and importance placed on breast milk feeds in the NICU, where younger preterm infants tend to outnumber late preterm infant admissions. As the incidence of late prematurity rises, breastfeeding rates within the late preterm population will likely become pivotal factors in reaching Healthy People 2010 goals of increasing breastfeeding to 75% initiation and 50% continuance at 6 months).[2].

Biological aspects

Human milk can be considered a species-specific biological "dynamic" system. Particularattention is given to specific bioactive and immunomodulatory factors, such as gastrointestinal hormones, immunoglobulins, lactoferrin, lysozyme, oligosaccharides, nucleotides, growth factors, enzymes, antioxidants and cellular components that can not only ensure adequate host defense against infections, but also actively modulate the immune response and modify the intestinal bacterial flora.Among these factors oligosaccharides have a relevant role. Originally described as a prebiotic "bifidus factor" that serves as a metabolic substrate for desired bacteria and shapes an intestinal microbiota composition with health benefits for the breast-fed neonate, today oligosaccharides are known to be more than just "food for bugs": literature shows that oligosaccharides also directly act preventing pathogen adhesion to infant mucosal surfaces, lowering the risk for infections, and modulate epithelial and immune cell responses Qualitatively and quantitatively, their presence in milk is strictly related to the expression of the mother's Se and/or Le genes: on these basis 4 different milk groups have been described. Substantial differences in oligosaccharide contents were found within the groups and were strictly related to the presence or absence of specific fucosyl-oligosaccharides. A recent study performed by our group reported new data on oligosaccharide concentrations in the 4 milk groups. These differences might exert an influence on several biological functions that are important for preterm infants and currently are attributed to milk oligosaccharides. But what was more striking was the higher concentrations of Human Milk Oligosaccharides (HMOs) in preterm compared with term milk. This highlights the relevant role of breastfeeding for preterm infants, who, because of the immaturity of their organs and systems, are at greater risk of contracting infectious illnesses. The different HMOs concentrations in preterm and term milk might represent a programmed adaptation of milk composition to the specific needs of the infants. Lower lactose concentrations in preterm milk compared with term milk were also described Low lactose concentrations in milk might have positive effects in preterm nutrition, becauselactose contributes to lower milk osmolality. Low levels also might represent lower substrate levels for the well-known lactase deficiency that is common among these newborns[3].Also the High levels of certain polyunsaturated fatty acids in breast milk (including eicosadienoic, arachidonic and gamma-linolenic acids) are associated with a reduced risk of child infection. Arachidonic acid and gamma-linolenic acid may also reduce viral shedding.

Benefits of Breastfeeding among Infants Born Prematurely

Given the morbidity statistics, it may appear counterintuitive to recommend breastfeeding as the optimal infant feeding method and engage in efforts to increase breastfeeding rates among late preterm mother-infant dyads. There could be lot of problems in the process of inadequate milk transfer, rather than product(breast milk),preterm infants who is not capable of good at sucking breast milk are supplemented with expressed breast milk, they do have better psychomotor, additionally, an extensive body. Research has elucidated the many specific benefits of breast milk for preterm infants, which, with its complex and temporally-variant composition dependent upon post-conceptionalage.Includes: enhanced gastrointestinal maturation; bolstered immunity demonstrated to decrease the incidence of necrotizing enterocolitis, other infections, and allergies; and acceleration of myelinization, possibly leading to improved childhood cognitive function.[4].

Urological, and cognitive outcomes in comparison to those feed on formulas feeding. Breastfeeding is protective against obesity, increasing up take of breastfeeding affects intake of calories and protein, insulin secretion and modulation of fat deposition and adipocyte development[5].Infants on breastfeeding do not get ill frequently. In addition to ensuring optimal nutrition, breast milk stimulates a number of elements such as immunoglobulins and growth factors, which is attributed to breast milk's immunological protection against minor infant ills, including otitis media and respiratory tract infection, which can decrease the expenses for frequently visiting hospitals and prescription for infants.[6]

Antioxidant is lower in the premature infants gestational age, oxidative stress causes cell damage during neonatal period that has been associated with disease as Necrotizing enterocolitis, chronic lung disease, Retinopathy, Periventricular leukomalacia, Intra ventricular hemorrhage. Breast milk is the food that contains antioxidants, in premature breastfed infants may be due, in part to a greater total antioxidant capacity in premature breast milk as compared to more mature breast milk or formula.[7]. Human brain development is a dynamic process that continues until the end of gestation. There is a critical period of brain growth and development that occurs in late gestation that is vital for the development of various neural structures and pathways. In fact, approximately 50% of the increase in cortical volume occurs between 34 and 40 weeks gestation, indicating that this is a very rapid period of brain growth. Preterm brain is only a fraction of the full-term brain weight and a significant proportion of brain growth, development, and networking occurs during the last six weeks of gestation. These tissues are vulnerable to injury during this critical time period of development. Injury may result in direct injury to developing tissues or disruption of critical pathways needed for neuronal and glial development.so the early breastfeeding in preterm help for the neuromotor development.[4]
Nutrients in breast milk, such the n-3 fatty acid docosahexaenoic acid (DHA), may benefit the developing brain. A major determinant of breast milk DHA content is the mother's diet, and fish is a rich source of DHA. In pregnancy, greater maternal fish intake – particularly fish low in mercury contamination is associated with better childhood cognitive outcomes, but the extent to which maternal fish intake during lactation accounts for the association of breastfeeding with cognition

OUT COME

Kangaroo mother care;

The skin-to-skin component of KMC where the infant is held upright between the mother's breasts in a nappy and hat, usuallycovered by a blanket, and in a private setting, compared with traditional care where contact between mother and infant is fully clothed. Comprehensive intervention of KMC comprising prolonged kangaroo skin-to-skin contact, early discharge and regular breastfeeding found no mortality or infectious morbidity, number of readmission after discharges and psychomotor development. Along with quality of mother to infant bounding.[8]

Benefit of breastfeeding preterm over gastro intestinal infection;

Factors like secretory IgA, oligosaccharides, lactoferrin and others available in breast milk may protect the infant from various infections through passive immunity. In vitro and in vivo binding studies have demonstrated that fucosylatedglycan in breast milk inhibit binding by campylobacter jejuni, stable toxin of enterotoxigenic Escherichia coli, and major strains of calciviruses (e.g., noroviruses (also known as Norwalk-like viruses)) to their target host cell receptors. One report suggests that glycoprotein lactoferrin found in breast milk protects against rotavirus infection.[9]. It has been shown that for preterm, growth-restricted and sick neonates including those requiring surgery, the use of breastmilksubstitutes is associated with increased short- and long-term adverse outcomes including mortality and serious morbidity. Epidemiological studies,and randomized and quasi-randomized controlled trialsin high-risk environments have found that the incidence of invasive infection is higher in low birthweight infants who are fed formula. A meta-analysis of randomized controlled trialshas shown that formula-fed low birthweight infants have five times the risk of necrotizingenterocolitis (NEC), a condition associated with a mortality of approximately 20% and significant long-term health-care costs amongst survivors. [10].

Necrotizing enterocolitis (NEC) is the most frequent and lethal disease of the gastrointestinal tract of preterm infants. At present, NEC is thought to develop in the premature host in the setting of bacterial colonization, often after administration of non-breast milk feeds, and disease onset is thought to be due in part to a baseline increased reactivity of the premature intestinal mucosa to microbial ligands as compared with the full-term intestinal mucosa.[11]
The increased reactivity leads to mucosal destruction and impaired mesenteric perfusion and partly reflects an increased expression of the bacterial receptor Toll-like receptor 4 (TLR4) in the premature gut, as well as other factors that predispose the intestine to a hyper-reactive state in response to colonizing microorganisms. The increased expression of

TLR4 in the premature gut reflects a surprising role for this molecule in the regulation of normal intestinal development through its effects on the Notch signalling pathway.[12] Despite the complex and multifactorial nature of the pathogenesis of NEC, three major risk factors have been implicated in its development: prematurity, bacterial colonization of the gut and formula-feeding.[13] Although no specific genetic predisposition has been clearly associated with NEC, studies evaluating concordance rates in monozygotic and dizygotic twins have found a familial predisposition for the disease. [14]Moreover, evidence suggests that genetic variants leading to upregulated expression of downstream signalling regulators of Toll-like receptor 4 (TLR4), an innate immune receptor that recognizes lipopolysaccharide found in Gram-negative bacteria, could lead to increased susceptibility to the disease. These signalling regulators include nuclear factor κB1, single Ig IL-1- related receptor,[15] the co-receptor molecule lymphocyte antigen 96 and the small glycolipid transport protein ganglioside GM2 activator. In addition, a single nucleotide polymorphism in the promoter region of IL18 and genetic variants encoding proteins linked to the regulation of the immune phenotype shift from type 1 to type 2 T helper cellscould all influence the risk of NEC development.[16]

Neonatal necrotizing enterocolitis (NEC) is a major cause of morbidity in preterm infants. We hypothesize that the intestinal injury in this disease is a consequence of synergy among three of the major risk factors for NEC: prematurity, enteral feeding, and bacterial colonization. Together these factors result in an exaggerated inflammatory response, leading to ischemic bowel necrosis. Human milk may decrease the incidence of NEC by decreasing pathogenic bacterial colonization, promoting growth of nonpathogenic flora, promoting maturation of the intestinal barrier, and ameliorating the proinflammatory response.[17]

Benefit of breastfeeding over cognitive development in preterm

Several additional factors support a specific value of breast-feeding with respect to cognitive function. First, breast-fed children appear to have a broad range of enhanced brain functions compared with formula-fed children. In addition to improved performance on a variety of different tests of cognitive function, indicating a general enhancement of cognitive function rather than of very specific functions, breast-fed children, compared with formula-fed children, show more rapid maturation of visual function and may acquire motor skills at an earlier age, It has also been suggested that breast-fed children have fewer emotional or behavioral problems and fewer minor neurologic problems later in life than do formula-fed children. These observations suggest that breast-feeding specifically enhances global neurologic development. Second, the enhanced benefit observed for low-birth-weight infants again suggests that breast milk provides specific advantages to premature infants. Third, the "dose effect," or increasing benefit with duration of breast-feeding, also suggests that there are specific advantages related to increasing exposure to breast milk.[18]

Prebiotics

Breastfeeding preterm infants have predominance of lactobacilli and bifidobacterimbifidum

Breastfeeding was hypothesized to mediate protection of the preterm through milk components that specifically supported colonization by *L. bifidus*. Which in turn, acidified the gut, bound to potential sites for colonization, and thereby inhibited pathogens from colonizing the gut and causing disease. Other types of indigestible oligosaccharides from other sources have since been found to stimulate colonization by *B. bifidum*and several lactobacilli. When fed in the diet, such materials stimulate gut colonization by beneficial microbes, presumably promoting health, and are known as prebiotics. Human milk, through its oligosaccharides, acts as a prebiotic. Breast- feeding may also introduce probiotics into the digestive tract of the nursing infant, thereby protecting the infant from infectious disease.[19].

Development of Intestinal mucosal immunity by breastfeeding:

Preterm infants, is hypersensitive to pro inflammatory stimuli and vulnerable to pathogens. Human milk contains immunomodulatory molecules that quench proinflammatoryprocesses, large numbers of quiescent leukocytes of unknown function, and glycans, some of which promote colonization by symbionts and others that inhibit specific pathogens. Many immunomodulatory molecules have been identified in human milk. TNF- receptors and interleukin (IL)-1RA (receptor antagonist) of milk effectively suppress proinflammatory TNF- and IL-1 activity, respectively, as does lactoferrin. Milk also contains anti- inflammatory cytokines IL-10 and transforming growth factor, and many antioxidants, protease inhibitors, prostaglandins, and other agents that may contribute to immunosuppression. Human milk factors

suppress induction of IL-8 expression (inflammatory response) in cultured intestinal epithelial cells; this suppression is greatest in immature cells, whose IL-8 response is more pronounced.[20]. These suppressive factors are at their highest concentrations in colostrum. Colostrum is consumed by neonates when priming and maturation of the mucosal immune system are greatest, and when the human gut can absorb macromolecules directly. An 80-kD protein from colostrum modulates the response by epithelial TLR-2, -4, and -5 to bacteria. Soluble CD14 mediates TLR-4 binding to lipopolysaccharide, the pattern recognition molecule of Gram-negative bacteria. Soluble CD14 concentrations are 20-fold higher in human milk than maternal serum; human milk-soluble CD14 may sensitize the innate mucosal immune system to Gram-negative bacteria, which include common pathogens of immature gut. Human milk also contains hormones, including epidermal growth factor, IGF, and leptin that can modulate the immune system of the intestinal mucosa *via* regulation of cytokine expression and other signaling pathways. Recently, adiponectin was found in human milk; adiponectin suppresses TNF- production in intestinal epithelium and macrophages. Human milk suppresses inflammation of the gut. Thus, the immature human gut may be hyperresponsive to specific stimuli that could result in mucosal damage, but human milk has a cornucopia of factors that can modulate inflammatory responses.[21].

Benefit of breastfeeding in ROP (Retinopathy of prematurity):

Preterm infants are at increased risk of ROP for at least two reasons. First, normal development of the retinal vascular system may be altered for the preterm infant growing in an extrauterine environment. Second, oxygen toxicity resulting from required oxygen administration to the VLBW infant is one ofthefactors that lead to abnormal development of the vascular tissue, resulting in retinal traction and retinal detachment.

Naturally human milk component contain Inositol. Inositol administration to preterm infants, however has resulted in a lower incidence of ROP. The protein content of preterm human milk is higher than term breast milk. Human milk from mothers of preterm infants is also higher in calories, sodium, and chloride than milk from mothers of term infants. In particular, the antioxidant components of human milk, including inositol, vitamin E, and beta - carotene may protect against the development of ROP. [22].

Breastfeeding and UTI;

The incidence of primary urinary tract infection (UTI) is greatest in the first month of life and decreases with age throughout childhood. Importantly, breastfeeding was significantly associated with a lower risk of UTI. Breast milk has been reported to have a protective effect against many infections in the first year of life, including gastroenteritis, acute otitis media, pneumonia, bacteremia, and meningitis. Research indicates that UTIs are caused by bacteria that migrate from the gastrointestinal tract and ano-genital area and colonize the lower urinary epithelium. The protective effect of breast milk is attributed to its action on the intestinal flora. Breast milk contains a high concentration of immunoglobulin A, which inhibits the adherence of bacteria to the intestinal mucosa and the urinary epithelium .In addition to antibacterial and antiviral antibodies, which protect the infant's gastrointestinal tract, lactoferrin prevents the growth of intestinal *E. coli.* Furthermore, the low pH of the stool of breast-fed infants provides a favorable environment for the growth of bifidobacteria and lactobacilli, which also protect the gastrointestinal tract from *E. coli* infection. While the protective effect of breastfeeding against UTI was shown in older infants and children as similar effect in premature infants .The protective effect of breast milk against *E. coli* infection may explain the predominance of *Klebsiella* isolates identified by urine and blood culture. Another possible explanation for the predominance of *Klebsiella* may be that hospitalized premature infants are colonized with these hospital gram-negative strains rather than with *E. coli*.[23]

Psychological benefits of breastfeeding;

The psychological benefits of breastfeeding should not be underestimated either; direct breastfeeding and providing the mother's own breast milk to a vulnerable and sick preterm infant may make an important tangible contribution. Providing breast milk may symbolize a deeper contact with the infant and may be one of the few activities under the mother's direction while the infant is in the NICU. Breastfeeding is associated with greater mother-infant attachment, which is sometimes threatened because of the separation of the mother and her preterm infant. In addition, maternal empowerment and self-confidence are increased in breastfeeding mothers. Furthermore, breastfeeding may have positive association with mother-infant interaction, which may be especially important for infants born preterm. [24]

Colostrum as oral immune therapy;

The unique properties of human milk provide the neonate with "immunologic, anti-infective, anti- inflammatory, epigenetic, and mucosal membrane protecting properties.Human colostrum has higher concentrations of secretory IgA, growth factors, lactoferrin, anti-inflammatory
cytokines, oligosaccharides, antioxidants, and other protective components as compared with mature human milk.

In a theoretical paper describing the foundation for how colostrum works as immune therapy, described in detail how the composition of colostrum stimulates the immature neonatal immune system by a prebiotic mechanism. Through lymphoid tissue in the oropharynx and the gut, colostrum stimulates immune development. When infants are fed via nasal gastric tube, the immune benefits of human milk bypass the oral- pharyngeal mucosa-associated lymphoid tissue. When given oropharyngeally, cytokines in the OMC interact with lymphoid cells in the lymphoid tissue in the mouth. Absorbing the immunologic factors via the oral mucosa stimulates the immune system systemically and promotes the mucosal differentiation in the gut and thus, developing the protective gut immune barrier. Stimulation of both the oral-pharyngeal mucosa-associated lymphoid tissue and the gut-associated lymphoid tissue is important to best overall immune development.

Lactoferrin is an important protein present in high concentrations in colostrum; these levels are even higher when a mother delivers prematurely. Lactoferrin, a glycoprotein and oligosaccharide (ie, prebiotic) found in colostrum, supports the innate immune response to maintain a wide range of physiologic norms.It has antimicrobial, anti-inflammatory, and immunomodulatory functions. Interestingly, lactoferrin binds to iron, preventing pathogenic organ- isms from obtaining iron from the infant necessary for their survival.There have been several small clinical trials showing that lactoferrin decreases the incidence of lower respiratory tract infections, the duration of dehydrating diarrhea, the severity of rotavirus infection, and the colonization with giardia in infants.Despite the significant evidence of the benefit of human milk for this vulnerable population, lactation rates for these infants in the NICU are limited.No parent is prepared to have their newborn cared for in the NICU. It is extremely difficult to maintain the necessary pumping regimen needed to ensure adequate milk production when parents cannot freely touch or hold their newborn. In addition to being concerned on a daily basis for the life of her infant, a mother must rely on a mechanical breast pump, pumping at least 8 times each day to establish and maintain an adequate milk supply.[25]

Conclusion

This article has reviewed literature in relation to the benefits and outcomes of breastfeeding for preterm infants in neonatal intensive care unit. Showing the numerous beneficial outcome of breastfeeding.

The importance of breastfeeding in the early period of life in neonatal intensive care unit in preterm infant is considered not simply in term of meeting immediate nutritional needs but also for its potentially long- lasting or life- long biological effects. The target is to achieve low birth weight infant's growth potential and to ensure their good health and a normal physiological and neurological outcome along with feeding tolerance, decrease the rate of neonatal sepsis, with high IQs, and increased intelligence. Although a high protein intake undoubtedly will improve growth and possibly reduce neurodevelopmental deficits, mother should be encouraged to supply milk and feeding immature infants, promoting early breastfeeding success for preterm infant and mother dyads in all expect of healthy life.

Table1

caption a7

Morbidity & Re-Hospitalizations among Late Preterm Breastfed Infants.

Reference/Design	**Study Purpose**	**Sample**	**Results/Effect Sizes Specific to Breastfeeding Morbidity**	**Limitations**	**Recommendations**
Tomashek et al. (2006) Retrospective chart review	Evaluate differences in hospital readmissions	24,320 FTIs (≥ 37 wks gest.) and 1,004 LPIs (34-36 6/7 wks	Breastfed LPIs compared to breastfed FTIs: **aRR 1.8 (1.2-2.6)** for observational stay *or*	Breastfeeding status defined only at time of birth certificate completion	Individualized discharge instructions and close follow-up for

U.S.	& observational stays between FTIs and LPIs	gest.) discharged < 2 days pp	hospital readmission **aRR 2.2 (1.5-3.2)** for hospital readmission aRR 1.3 (0.6-2.9) for observational stay	Unable to link all readmissions and birth records Secondary data sources Exclusion of multiples	breastfed LPIs Research to establish discharge & follow-up guidelines for breastfed LPIs
Shapiro-Mendoza et al. (2006) Retrospective chart review U.S.	Compare hospital readmissions and observational stays (i.e., morbidity) & mortality between healthy LPIs with/out risk factors	9,552 "healthy" vaginally-delivered infants 34-36 6/7 wks gest.	Overall neonatal morbidity among breastfed LPIs, compared to non-breastfed LPIs: **aRR 1.65 (1.33-2.04)** * Mortality statistics not calculated due to low incidence	Breastfeeding status defined only at time of birth certificate completion Unable to link 23% of rehospitalizations to birth records Secondary data sources Exclusion of multiples	Closer hospital monitoring & follow-up of breastfed LPIs, especially with risk factors, including: Asian/Pacific Islander heritage, firstborn status, labor and delivery complications
NO EXCLUSIVE CATEGORY FOR INFANTS 34 0/7-36 6/7 WEEKS GESTATION					
Wang et al. (2004) Retrospective chart review U.S.	Test hypothesis that NTIs have more medical problems pp than FTIs	120 NTIs (35-36 6/7 wks gestation) & 125 FTIs (≥ 37 wks gest.) *~80% breastfeeding rate*	Discharge delay due to "poor feeding:" NTIs: 75.9%; FTIs 28.6%: NTIs compared to FTIs, calculated **OR 7.9 (1.2-49.9), p = 0.029**	Gestational classification of NTI differs from LPI No objective identification of breastfeeding status or success at time of discharge Secondary data sources	Ongoing breastfeeding assistance and support for NTIs Early supplementation with expressed breast milk or formula, if indicated Close observation for common NTI feeding complications; consider longer pp hospitalizations
Bhutani& Johnson (2006) Retrospective review U.S.	Comparison of etiology and clinical outcomes between LPIs and FTIs with a diagnosis of kernicterus or extreme	96 FTIs (≥ 37 wks gest.) and 29 LPIs (35-36 6/7 wks gest.) part of Pilot Kernicterus Registry *"Nearly all" LPIs*	Severe posticericsequelae: LPIs: 82.7%; FTIs: 70.8% **(p< 0.01)** "Unsuccessful lactation experience" most common risk factor for hazardous hyperbilirubinemia in LPIs	Sample not inclusive of full late preterm period No distinction among	Assessment of pre-discharge hyperbilirubenemia risk; follow-up within 24-48 hrs for LPIs Family-

	hyperbilirubinemia	*breastfeeding*		breastfed/ non-breastfed LPI infants; breastfeeding in term infants not addressed "Unsuccessful lactation experience" not defined	centered care streamlined between hospital & pediatrician office Accurate, precise, universally available hyperbilirubinemia measures

Table 2
caption a7
Initiation, Duration, & Exclusivity of Breastfeeding among Late Preterm Mother-Infant Dyads.

Reference/Design	**Study Purpose**	**Sample**	**Results/Effect Sizes Specific to Breastfeeding Patterns**	**Limitations**	**Recommendations**
Tomashek et al. (2006) See Table 1	See Table 1	See Table 1	Breastfeeding at hospital discharge: LPIs: 59.3% (n= 592) FTIs: 69.4% (n= 16,864) LPIs compared to FTIs, calculated **OR 0.64 (0.56-0.73)**	See Table 1	See Table 1
Shapiro-Mendoza et al. (2006) See Table 1	See Table 1	See Table 1	LPIs breastfeeding at hospital discharge: **70.0%** (n = 6,651)	See Table 1	See Table 1
NO EXCLUSIVE CATEGORY FOR INFANTS 34 0/7-36 6/7 WEEKS GESTATION					
Merewood et al. (2006) Retrospective chart review U.S.	Compare breastfeeding initiation rates among preterm and term infants	67,884 singleton births between 24-42 wks gestation	Rates of breastfeeding initiation: 24-31 wks gest.: 62.9% 32-36 wks gest.: 70.1% 37-42 wks gest.: 76.8% "Older preterm" (32-36 6/7 wks gest.) as compared to FTI (37-42 wks gest.): **aOR 0.73 (0.68-0.79)**	No exclusive LPI category Self-report of breastfeeding status via single, double-barreled question Some factors not controlled for (e.g., infant morbidity)	Provision of additional knowledge, support, and equipment (e.g., breast pumps) for breastfeeding preterm dyads breastfeeding practices or interventions for all

				Exclusion of multiples Secondary data sources	gestational ages should consider maternal birthplace and race
Colaizy&Morriss (2008) Retrospective review of survey data U.S.	Test hypothesis that NICU admission reduces breastfeeding in U.S. infants	29,940 NICU-admitted infants part of 2000-2003 PRAMS survey	Infants 32-< 35 wks gest., NICU-admitted (n = 4949) vs. non-admitted (n = 467): *Ever breastfed:* 70.2% vs. 55.3% **(*p*< 0.01)** *Breastfed > 4 wkspp:* 49.1% vs. 35.1% **(*p*< 0.01)** Infants 35-< 38 wks gest. NICU-admitted (n = 8159) vs. non-admitted (n = 9601): *Ever breastfed:* 68.7% vs. 64% **(*p*< 0.01)** *Breastfed > 4 wkspp:* 47.6% vs. 43.5% **(*p*< 0.01)** Compared to infants ≥38 wks gest., breastfeeding > 4 wkspp: **OR 0.87 (95% CI 0.78-0.97)** infants 32-<35 wks gest. **OR 0.78 (95% CI 0.73-0.83)** infants 35-<38 wks gest. *(lowest OR of any gestational cohort, including infants < 32 wks)*	No exclusive LPI category Self-report of all data	Further research investigating factors within the NICU environment that are associated with successful breastfeeding initiation and continuation, especially among LPI (35-<38 wks gest.)
Donath& Amir (2008) Population-based cohort study **Australia**	Investigate effect of gestation on initiation and duration of breastfeeding	3,600 singleton infants in Australia	NTI (35-36 6/7 wks gest.) breastfeeding rates &aOR's compared to infants ≥ 40 wks gest: Initiation: 88.2% aoR 0.64 (0.35-1.18) 6 months pp: 41.2% **aOR 0.51 (0.34-0.76)** **Lower rates for NTIs than for any other gestational age (e.g., ≤34 wks, ≥37 wks)*	No category inclusive of full late preterm period May not be representative of U.S. rates Exclusion of multiples Significance/effect size not reported for NTI compared to early PTI	Individualized assessment and discharge planning for infants of 35-36 gestational weeks to improve chances of successful breastfeeding Need for awareness among clinicians that infants less than 40 weeks gestation (even 37-39 weeks) may be

					less likely to achieve successful breastfeeding
Wooldridge & Hall (2003) Ex post facto descriptive correlational **Canada**	Describe breastfeeding patterns of moderately preterm infants over 4 wkspp	66 infants 30-35 6/7 wks gest. from 53 mothers in Canada	According to feeding diaries, rate of breastfeeding exclusivity: 1wk pp: 60.6% 4 wkspp: 59.1% Rate of exclusive & "primary" breastfeeds at breast increased steadily over 4 wkspp: 3% to 23% (exclusive); 18% to 27% (primary) Little variability in rates of breastfeeding exclusivity over 4 wkspp when breastfeeds not necessarily at breast	No exclusive LPI category May not be representative of U.S. rates Small sample size, convenience sampling Possible rate inflation due to breastfeeding experience of research assistants 40% of sample was twins; non-comparable to other included studies Effect sizes/significance not reported	Establishment of adequate milk supply before hospital discharge in moderately preterm mother-infant dyads More research examining breastfeeding patterns and best practices among moderately preterm twins; more clinical breastfeeding support for mothers of twins
Makeovers et al. (2002) Randomized controlled trial **Canada**	Compare effects of breastfeeding support in hospital & home settings on breastfeeding outcomes and satisfaction in FTIs and NTIs	75 FTIs (≥38 wks) and 37 NTIs (35-37 6/7 wks gest.) breastfeeding at hospital discharge	Breastfeeding exclusivity (past 24 hrs) at 5-12 days pp in standard care group: NTIs: 67.7% (n=12) FTIs: 73.5% (n=34) NTIs compared to FTIs, calculated OR 0.72 (0.17-2.98)	No exclusive LPI category Very small sample of NTIs Short follow-up period Inclusion criteria requiring breastfeeding at discharge may inflate exclusivity rate May not be representative of U.S. rates	Awareness that many NTIs require supplemental feeding after discharge, contributing to decreased breastfeeding exclusivity in this grp Research to determine optimal healthcare setting, frequency, and duration of support for breastfeeding mothers Healthcare policies to ensure availability of skilled, in-home lactation support for all breastfeeding mothers

1. Taylor, S.N., et al., *Intestinal permeability in preterm infants by feeding type: mother's milk versus formula.* Breastfeed Med, 2009. 4(1): p. 11-5.
2. Radtke, J.V., *The paradox of breastfeeding-associated morbidity among late preterm infants.* J Obstet Gynecol Neonatal Nurs, 2011. 40(1): p. 9-24.
3. Bode, L., et al., *Overcoming the limited availability of human milk oligosaccharides: challenges and opportunities for research and application.* Nutr Rev, 2016. 74(10): p. 635-44.
4. Adams-Chapman, I., *Neurodevelopmental outcome of the late preterm infant.* Clin Perinatol, 2006. 33(4): p. 947-64; abstract xi.
5. Owen, C.G., et al., *Effect of infant feeding on the risk of obesity across the life course: a quantitative review of published evidence.* Pediatrics, 2005. 115(5): p. 1367-77.
6. Ball, T.M. and A.L. Wright, *Health care costs of formula-feeding in the first year of life.* Pediatrics, 1999. 103(4 Pt 2): p. 870-6.
7. Robles, R., N. Palomino, and A. Robles, *Oxidative stress in the neonate.* Early Hum Dev, 2001. 65 Suppl: p. S75-81.
8. Charpak, N., et al., *Kangaroo mother versus traditional care for newborn infants </=2000 grams: a randomized, controlled trial.* Pediatrics, 1997. 100(4): p. 682-8.
9. Feachem, R.G. and M.A. Koblinsky, *Interventions for the control of diarrhoeal diseases among young children: promotion of breast-feeding.* Bull World Health Organ, 1984. 62(2): p. 271-91.
10. Boyd, C.A., M.A. Quigley, and P. Brocklehurst, *Donor breast milk versus infant formula for preterm infants: systematic review and meta-analysis.* Arch Dis Child Fetal Neonatal Ed, 2007. 92(3): p. F169-75.
11. Neu, J. and W.A. Walker, *Necrotizing enterocolitis.* N Engl J Med, 2011. 364(3): p. 255-64.
12. Salhab, W.A., et al., *Necrotizing enterocolitis and neurodevelopmental outcome in extremely low birth weight infants <1000 g.* J Perinatol, 2004. 24(9): p. 534-40.
13. Good, M., et al., *Breast milk protects against the development of necrotizing enterocolitis through inhibition of Toll-like receptor 4 in the intestinal epithelium via activation of the epidermal growth factor receptor.* Mucosal Immunol, 2015. 8(5): p. 1166-79.
14. Bhandari, V., et al., *Familial and genetic susceptibility to major neonatal morbidities in preterm twins.* Pediatrics, 2006. 117(6): p. 1901-6.
15. Sampath, V., et al., *SIGIRR genetic variants in premature infants with necrotizing enterocolitis.* Pediatrics, 2015. 135(6): p. e1530-4.
16. Treszl, A., et al., *Lower prevalence of IL-4 receptor alpha-chain gene G variant in very-low-birth-weight infants with necrotizing enterocolitis.* J Pediatr Surg, 2003. 38(9): p. 1374-8.
17. Claud, E.C. and W.A. Walker, *Hypothesis: inappropriate colonization of the premature intestine can cause neonatal necrotizing enterocolitis.* Faseb j, 2001. 15(8): p. 1398-403.
18. Lucas, A., et al., *Early diet in preterm babies and developmental status in infancy.* Arch Dis Child, 1989. 64(11): p. 1570-8.
19. Gyorgy, P., et al., *Undialyzable growth factors for Lactobacillus bifidus var. pennsylvanicus. Protective effect of sialic acid bound to glycoproteins and oligosaccharides against bacterial degradation.* Eur J Biochem, 1974. 43(1): p. 29-33.
20. Claud, E.C., T. Savidge, and W.A. Walker, *Modulation of human intestinal epithelial cell IL-8 secretion by human milk factors.* Pediatr Res, 2003. 53(3): p. 419-25.
21. Labeta, M.O., et al., *Innate recognition of bacteria in human milk is mediated by a milk-derived highly expressed pattern recognition receptor, soluble CD14.* J Exp Med, 2000. 191(10): p. 1807-12.

22. Hylander, M.A., et al., *Association of human milk feedings with a reduction in retinopathy of prematurity among very low birthweight infants.* J Perinatol, 2001. 21(6): p. 356-62.
23. Levy, I., et al., *Urinary tract infection in preterm infants: the protective role of breastfeeding.* Pediatr Nephrol, 2009. 24(3): p. 527-31.
24. Callen, J. and J. Pinelli, *A review of the literature examining the benefits and challenges, incidence and duration, and barriers to breastfeeding in preterm infants.* Adv Neonatal Care, 2005. 5(2): p. 72-88; quiz 89-92.
25. Gephart, S.M. and M. Weller, *Colostrum as oral immune therapy to promote neonatal health.* Adv Neonatal Care, 2014. 14(1): p. 44-51.