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Progress Towards Evidence-Based Nutrition

Scientific Advancement and Clinical Experience with a Human Milk Diet in the N/PICU

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*William Rhine, MD*
Welcome and Opening Remarks

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The 1st Annual International Conference on Human Milk Science and Innovation brought together scientists from around the world to see a whole new vision for infant nourishment and protection in the neonatal/perinatal intensive care unit (N/PICU) for the 21st century. During this 2-day program, scientists and clinicians on the cutting edge of evidence-based nutrition research discussed advances and identified future opportunities in nutrition science. Emphasis was placed on application of these advances to the clinical use of human milk in order to achieve long-term health and well-being of the youngest members of society.

The 20th century saw tremendous advances in science brought about by the discipline of chemistry, which virtually transformed the human condition. At its core, this reductionist science allows us to study systems that are the sum of their parts, making it possible to predict and manage what happens when the components are mixed in various proportions.

However, when it comes to studying human systems, we are more than the sum of our parts. To meet this challenge, the integrative science of biology has assumed the core role. Today, chemistry, mathematics and engineering are guided by and actively adding to our biological understanding of the human genome. Even the discipline of nutrition has launched the field of nutrigenomics in order to identify and understand molecular-level interactions between nutrients, other dietary factors and the human genome.\(^1\) Clearly, the environment we are exposed to very early in life has persistent effects.\(^2\) For example, we now know that a poor diet early in life predisposes individuals to metabolic disease later in life.\(^3\)

I am pleased to have co-chaired this inaugural expert opinion session with my colleague, William Rhine, MD. This proceedings was conceived to capture and disseminate the highlights of this event. It is our hope that the information presented here will raise interest and awareness in infant nutrition and inspire healthcare professionals who practice in N/PICUs to explore and incorporate the benefits of human milk into clinical practice. We would like to thank the sponsor, Prolacta Bioscience, for supporting this endeavor.

References

The earliest mammary function, perhaps even prior to providing nutrition, was to provide protective immunoglobulins to offspring in support of survival. Milk is an individualized, structured nutrient delivery system principally composed of water, lipids, protein (largely casein and whey), and the carbohydrate lactose and other oligosaccharides. Over time, its composition has evolved and been individualized to meet the needs of successive generations of mammalian infants receiving it.

Though simple in concept, the process of producing and transferring appropriate amounts of the essential nutrients from the maternal diet and body stores to the infant through lactation is daunting. The bioavailability of most nutrients from food materials is poor owing to their insolubility, reactivity or complexity. Furthermore, absorption of nutrients varies in response to the presence and concentrations of other nutrients in the diet.1

Today we recognize that a wide diversity of lactation strategies exists and all are influenced by the biology of the mother and infant, as well as by ecological demands during infant feeding. Variations in milk composition and function across species presumably reflect the need to adapt to these and other factors, including an environmental niche, a reproductive strategy, and the nutrient and growth requirements of the neonate.2

Advances in the Genomics of Mammalian Milk
Tools of genomics are making it possible to understand infant nourishment as never before and to provide premature infants with a better path toward lifelong health. Results of research at the University of California at Davis (UC Davis) and elsewhere provide insight into understanding the discrete functions of milk and the success of mammalian infants in a hostile world. We know that the biological genesis of milk production in mammals is ancient, and the evolution of milk has been constrained to maximize survival of both mothers and offspring.3

Individual milk and milk-production genes occur across a broad range of mammalian species, with 38 DNA segments associated with particular traits. These segments probably did not change as new species evolved.

Aside from small subsets of proteins such as the major milk proteins, there is no sudden transcriptional switch around the time of parturition. Genetic transcriptional changes occur gradually during progression of the reproductive stage until involution, with the onset of lactation primarily controlled by post-transcriptional mechanisms.4

Because milk is produced for offspring at great physiological expense to the mother, it is likely that today, as in the past, there are few superfluous components in milk. Each succeeding generation of mammals has produced more nourishing milk in order to ensure the survival and reproductive success of their offspring.

Functions of Milk
Human milk is unique in that it plays an important role in multiple aspects of infant development that extend beyond “simple” nutrition. The earliest mammary function, perhaps even prior to nutrition, was to provide protective immunoglobulins to offspring in support of survival (Table 1).5 In fact, through a range of mechanisms, human milk is the only drug or nutritional substance that simultaneously reduces inflammation while increasing the activity of the immune system for its surveillance role (Table 2). Human milk is unique in this regard, and this characteristic might be the most important function of milk as it relates to future research in health and disease treatment.
Table 1. Contributions of milk as a biological strategy.

- Nourishment of the infant
- Disease defense for the infant and mother
- Regulation/stimulation of infant development
- Regulation/stimulation of maternal mammary tissue development, growth and function
- Inoculation, colonization, nourishment, regulation and elimination of infant and maternal mammary microflora

Table 2. Mechanisms whereby human milk simultaneously reduces inflammation while increasing the activity of the immune system.

- Suppress hyperactivation of immune cells through toll-like receptors
- Alter microbiota (gut flora)
- Maintain barrier integrity
- Minimize “excess” adipose stimulation of human monocyte–derived macrophages

Future Challenges in Human Milk Research

The composition of human milk is complex, individualized and not precisely duplicated by other sources, with energy density (kcal/g) being the biggest difference across primates. In recent studies, varying the composition of milk shows that changes in the normal process of lactation and feeding affects the size and behavior of the infant. For example, in the early postnatal period, heavier rhesus monkey mothers with more reproductive experience produce higher available milk energy (milk energy density [kcal/g] x milk yield [g]). In response, infants switched from lower to higher milk energy density during the early postnatal period show higher activity and greater confidence in a stressful setting later in infancy. Importantly, these changes persist after the end of lactation.

Conclusions

The challenge for future researchers is to confirm these findings on milk quality, size and behavior in humans and address important questions of the effect of an infant’s diet on the full spectrum of social, psychological and health-related aspects of later life.

References


Oligosaccharides and Bifidobacteria in the Human Infant and Beyond

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Human milk oligosaccharides are a natural source of prebiotics in infants and selectively amplify bacterial populations, including the growth of Bifidobacteria.

Aside from its nutritional and immunological protective components, a third component of milk develops inside the infant. This might be referred to as the milk-oriented microbiota (MOM).

This third level of defense includes oligosaccharides, a component of glycoproteins or glycolipids. Each contains localized regions on their surface (epitopes) that serve as pathogen
adhesion sites in the human gastrointestinal tract and on other epithelial cell surfaces to competitively bind and remove disease-causing micro-organisms before they cause infection.

Importance of Oligosaccharides and Bifidobacteria

Much metabolic research focuses on the contribution of oligosaccharides to the selective growth of bifidobacteria. Following birth, *Staphylococcus*, *Streptococcus* and *Enterobacteriacea* colonize the intestinal tract of the neonate. This is rapidly followed by a transition to bifidobacteria and other obligate anaerobes such as *Bacteroides* and *Clostridium*, a process influenced by the source of nutrition.  

1

Human milk is the optimal source of human nutrition because of its elements that benefit the neonate, including oligosaccharides, protein and immune factors.  

2

Human milk oligosaccharides (HMO) are a natural source of prebiotics in infants and selectively amplify bacterial populations, including the growth of bifidobacteria.  

3,4

In addition, HMOs exhibit anti-adhesive effects that reduce the binding of pathogenic bacteria to gastrointestinal mucosa. Interestingly, these anti-adhesive carbohydrates are not bactericidal, making the spread of antibiotic-resistant pathogens less likely to occur.  

5

Human milk/colostrum contains between 5 and 23 g/L of these oligosaccharides, with over 200 different HMO structures.  

6

The *B. longum* subsp. *infantis* (*B. infantis*) ATCC15697 genome features five distinct gene clusters with predicted capacity to bind, cleave and import milk oligosaccharides.  

7 Thus, *B. infantis* ATCC15697 offers a competitive nutrient-utilization strategy that targets milk-borne molecules lacking in a nutritive value to the neonate.

Advances in Research

The important question from a clinical perspective is whether this knowledge might be applied to improved infant care in the neonatal/perinatal intensive care unit (N/PICU). Research from the University of California at Davis Foods for Health Institute suggests that the answer may be yes with respect to the ability to colonize the gastrointestinal tract.

In one recent study,  

8 premature formula-fed infants were randomly assigned to receive either *B. infantis* or *B. lactis* (HMO negative control). A second phase evaluated *B. infantis* or *B. lactis* in breast milk-fed vs. formula-fed premature infants.

*B. infantis* was more effective at colonizing the fecal microbiota than *B. lactis* in both formula-fed and human milk-fed premature infants. Figure 1 illustrates the response to feeding *B. infantis* with breast milk on establishing bifidobacteria compare to *B. lactis*. The combination of human milk plus *B. infantis* resulted in the greatest fecal levels of bifidobacteria. In addition, levels of potentially harmful bacteria, known as γ-Proteobacteria, decreased in the breast milk-fed babies who received *B. infantis*. On the other hand, formula-fed infants treated with *B. infantis* and *B. lactis* did not experience a decline. γ-Proteobacteria typically increases at the onset of necrotizing enterocolitis (NEC) and can cause serious tissue-damaging infections in the gastrointestinal system, lungs, and other organs of the body.  

8

It is reported that the mechanism for bifidobacteria to modulate host defense responses, in an animal model, relates to acetate produced by protective bifidobacteria. Acetate improves intestinal defenses through improved barrier function mediated by epithelial cells and thereby protects against infection.  

9 Evidence in humans suggests a similar protective mechanism.

Conclusions

Evidence suggests that bifidobacteria is a natural part of milk, and the glycan repertoire in human milk exert their impact on the infant gastrointestinal microbiota. The best outcomes occur when bifidobacteria (*B. infantis*) is combined with human milk. Human milk is the optimal source of human nutrition and any attempt to enrich human milk should ensure quality and consistency of the human components. Future research will determine its value in preventing diseases such as NEC in infants with dysbiosis.
**References**


**Pasteurization Effect on Bioactive Components of Donor Milk and an Update on Fecal Calprotectin to Measure Gut Inflammation**

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**Many bioactive molecules in breast milk may be diminished by pasteurization; however, they remain present.**

Human breast milk is the normal source of nutrition for infants. However, mothers of preterm infants face barriers to providing sufficient milk volume to their babies who are at risk for developing necrotizing enterocolitis (NEC). This review highlights research on gut health at the Mount Sinai and SickKids Hospitals (Toronto) and the University of Toronto, Canada as it pertains to bioactive components of donor milk and fecal calprotectin.

**Bioactive Components of Donor Milk Following Pasteurization**

Pasteurization (62.5°C, 30 min) to remove possible infectious contaminants is recommended before distributing donor human milk. This process also alters the levels of immune and bioactive components. For example, energy and fat levels change (-2.9% and -8.9% [P<0.05], respectively pre vs. post pasteurization), but this may reflect losing the rim of fat during each container change in the experimental process. Glucose and protein concentrations are not dramatically altered (1.4% [P<0.05] and <1.0%, respectively) following pasteurization.

Post-pasteurization, bile salt-dependent lipase — important for absorption of milk fat — is abolished. Immunoglobulin A (IgA) and lactoferrin are reduced by 30% to 50%. By comparison, bovine formulas contain no human IgA or lactoferrin.

Among cytokines thought to protect newborn infants against NEC, concentrations of some of these components of the immune system decline post-pasteurization. Growth factors thought to play a role in gut epithelial cell differentiation and division as well as in cell apoptosis (e.g., heparin-binding epidermal-like growth factor [HB-EGF], hepatocyte growth factor [HGF] and granulocyte colony-stimulating factor [GCF]) decline, but are still present. Similar changes occur with gangliosides, which are thought to protect against NEC.

In addition, adiponectin and insulin concentrations — hormones important for determining body mass index (BMI) and satiety — are lower but remain present following pasteurization.

**Calprotectin**

Calprotectin offers a model for studying inflammation in the gut of preterm infants. Calprotectin comprises 60% of leukocyte cytosolic protein. It has antimicrobial and antymycotic properties and is released by activated neutrophils in the presence of inflammation. Furthermore, calprotectin may be isolated in stool samples and serve as a biomarker of inflammation.
The relationship between NEC and cow’s milk formula for very low birth weight (<1500 g) infants is established. The best protection against NEC may be an exclusive human milk-containing diet. However, nutrient fortification of breast milk is required to meet the nutrient needs of very low birth weight infants. This is most frequently done using bovine-based fortifiers.

Studies are underway to determine the usefulness of calprotectin in the stool of very low birth weight infants as a research tool to study the impact of exposure to bovine protein and as a clinical tool in predicting the risk for NEC.

Conclusions
Evidence supports the important health benefits of bioactive molecules in human milk. The impact of pasteurization is less studied, but available data reveal that most bioactive components of pasteurized milk are maintained, albeit in some cases at lower concentrations. The continued presence of some proteins such as lactoferrin following pasteurization may be important in growth and development when compared to bovine formula.

References
Section 2: Clinical Research—Benefits of Human Milk for Premature Infants

Aggressive Use of a 100% Human Milk Diet to Achieve Better Growth: The Texas Children’s Hospital Experience

David J. Rechtman, MD* presented on behalf of Amy B. Hair, MD* and Steven A. Abrams, MD*
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Human milk feeding improves the health and development of premature infants, and the American Academy of Pediatrics recommends that all preterm infants receive human milk, including donor human milk if mother’s own milk is unavailable.

Human milk feeding for very low birth weight (VLBW) infants offers an alternative to bovine-based fortification of mother’s own milk or bovine-based formula. One study of exclusive human milk-based diet fortified with a donor human milk-derived fortifier revealed that an exclusive human milk-based diet in infants ≤1250g birth weight (BW) reduced the incidence of necrotizing enterocolitis (NEC) by 65% and the odds of surgical NEC by 8-fold.

Extremely premature infants are at risk for slow growth, metabolic abnormalities and poor neurodevelopmental outcomes. Yet, despite current strategies aimed at appropriate nutrition, many of these infants have postnatal growth failure (extrauterine growth restriction; anthropometric values less than 10th percentile). Clearly, growth velocities greater than current guidelines are needed to ensure that infants maintain their birth weight percentile on the growth curve and avoid extrauterine growth restriction.

The Texas Children’s Hospital Experience

Because of the potential benefits of an exclusive human milk-based diet, the growth in all of infants ≤1250g BW was evaluated. The hypothesis was that a feeding protocol providing an exclusive human milk-based diet with early and rapid advancement of fortification using a donor human milk-derived fortifier would meet growth standards in these infants and lead to decreased extrauterine growth restriction.

Preterm infants (N=104) weighing ≤1250g BW were fed an exclusive human milk-based diet until 34 weeks postmenstrual age. Human milk fortification with donor human milk-derived fortifier was started at 60 mL/kg/day and advanced to provide 6 to 8 additional kilocalories per ounce (or 0.21 to 0.28 kcal/g). Data for growth were compared to previous human milk-fed cohorts and historical growth standards at Texas Children’s Hospital.

Infants evaluated consecutively had a gestational age of 27.6±2.0 (mean ± SD) weeks and BW of 913±181g and demonstrated weight gain of 24.8±5.4 g/kg/day with length 0.99±0.23 cm/week and head circumference 0.72±0.14 cm/week.

Forty-nine infants (47%) received more than 90% mother’s own milk. At the time of discharge home, 7 infants (7%) were receiving only human milk and 39 infants (38%) were receiving any human milk. Weight velocity from birth to discharge was significantly affected by the day of fortification of feeds (P=0.005), days to reach full enteral feeds (P=0.02), and BW (P<0.001), but not gender or race.

When comparing growth rates of this cohort to human milk-fed cohorts by Sullivan et al, this cohort had significantly greater growth in weight (P<0.001) and length (P=0.008) but not in head circumference. Weight gain for this cohort was significantly higher than each of the other 3 groups in Figure 1; and the bovine human milk fortification (HMF) or formula group was significantly higher than the HMF 100 group, as was length growth. This cohort reached full feeds sooner, had fewer total parenteral nutrition (TPN) days, and earlier fortification of feeds (Fig. 1).

‡ Prolacta Bioscience played no role in the design, conduct or primary analysis of this study. All product used was purchased commercially.
There were 3 medical NEC cases and 1 surgical NEC case. Twenty-two infants (21%) were small for gestational age (SGA) at birth. Based on historical data at the Texas Children’s Hospital, prior to this protocol approximately 80% of appropriate gestational age (AGA) babies went home as SGA. Now, with 22% SGA babies at the start of the study, only 23% more with AGA status went home as SGA, a clinically significant improvement.

Overall, 45 infants (43%) had extrauterine growth restriction. Weight velocity was affected by day of fortification (P=0.005) and day of full feeds (P=0.02). This cohort, fed an exclusive human milk-based diet with early and rapid advancement of fortification using a donor human milk-derived fortifier, had significantly greater growth in weight and length compared to previous entirely human milk-fed cohorts.

**Conclusions**

A feeding protocol for infants weighing ≤1250g that provided an exclusive human milk-based diet with early and rapid advancement of fortification was associated with weight gain that exceeded targeted growth standards for length and head circumference. It is likely that early introduction and rapid advancement of human milk fortification in this protocol led to achievement of improved growth rates. Consistent nutritional policies using this approach may be considered for this population.

**References**


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**Figure 1. Outcomes in the current study** compared to results reported by Sullivan et al, 2010.†

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<th>Bovine HMF or Formula† (n=69)</th>
<th>Human milk + HMF 100† (n=67)</th>
<th>Human milk + HMF 40† (n=71)</th>
<th>Human milk + HMF 60* (n=104)</th>
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<td>Days to full feeds</td>
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Human Cream to Boost Calories in Breast Milk: Status of a Clinical Trial

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In clinical practice, donor human milk and mother’s milk frequently contain less than 20 kcal/oz, and standardization by donor milk banks is not guaranteed.

Over the last two decades, advances in medical care have improved outcomes for very low birth weight (VLBW; <1500g) infants. Evidence-based practices in neonatal intensive care units (NICUs) have decreased nosocomial infections, improved growth and decreased length of stay. As part of these advances, early administration of enteral feeding, preferably using mother’s own milk or pasteurized milk products if mother’s milk is unavailable, is on the rise.

Maximizing fortification helps increase weight gain by meeting caloric and macro-micronutrient needs. However, there may be uncertainty as to whether the actual nutrient content of human donor milk from a local milk bank provides the labeled 20 cal/oz. This is because the range of caloric density among mothers expressing milk for their infants varies as much as 29%. Variability in nutrients is also reported. A study of 650 pooled breast milk samples reported that all required adjustment of at least one macronutrient. On average, 0.3g of fat, 0.7g of protein and 1.2g of carbohydrate were added.

Although pooling milk reduces variability, standard fortification resulting in under- or over-nutrition remains a concern because either extreme confers risks in development. Accordingly, individualized fortification optimizes protein and energy intake.

Cream Supplement to Improve Rate of Growth
At the University of Texas, San Antonio, and Baylor College of Medicine, we are conducting a study designed to determine whether a cream supplement (Table 1) added to the usual nutritional feedings for VLBW infants would do no worse (lack of inferiority) than a group not fed cream as measured by weight gain and days of precision nutrition.

Table 1. Human Milk Cream.

| • Derived from pasteurized human milk and composed of 25% fat |
| • All production is conducted in ISO 8 and ISO 7 clean rooms |
| • The cream is measured for nutritional content and then diluted with permeate if necessary to formulate the caloric content to 2.5 cal/mL |
| • After formulation is complete, the product is pasteurized and filled in 10mL increments into a 30mL bottle |

Both sites use exclusive human nutrition for this population, with donor human milk purchased from different milk banks. Human milk cream is derived from pasteurized human milk and composed of 25% fat. The cream is measured for nutritional content and then diluted with permeate if necessary to formulate the caloric content to 2.5 cal/mL. The product is then pasteurized and filled in 10mL increments into a 30mL bottle. All production is conducted in ISO 8 and ISO 7 clean rooms.

The study protocol calls for 78 infants weighing between 750g and 1250g, with a reasonable expectation of survival through 36 weeks corrected gestational age. Following informed consent, enteral feeding begins before the 21st day of life, with adherence to a feeding protocol involving mother’s own milk/donor milk fortification using a human-based product (Prolact+H2MF®) and, potentially, human cream.

Inability to obtain consent prior to fortification, enrollment in another clinical study affecting nutritional management, or the presence of clinically significant congenital heart disease or other major congenital malformations, intestinal surgery, reasonable potential for early transfer to a non-study institution, or the inability to participate for any reason based on the decision of the study investigator are reasons for exclusion.

The primary outcome for the study is rate of weight gain from the initiation of enteral feed until the infant reaches 36 weeks.
corrected gestational age or is weaned off fortifier, whichever occurs first. Secondary outcomes include rate of change in head circumference and length over the same period, total amount of fortifier used and morbidity (i.e., late-onset sepsis and necrotizing enterocolitis).

Conclusions
The results of this collaborative study will be available in 2014. We anticipate that the findings will stimulate future studies of the response to cream supplementation and/or targeted fortification in larger populations and in high-risk populations for growth restriction such as infants weighing less than 750g and infants with intestinal disease.

References

Human Recombinant Lactoferrin Prophylaxis in Very Low Birth Weight Infants: Status of a Clinical Trial

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Lactoferrin is a multifunctional protein that influences intestinal homeostasis in human milk. It is bacteriostatic and bactericidal and provides immunomodulation in innate host defenses, including promoting a mature and healthy gut.

Lactoferrin has the potential to impact the microbiome prior to and after milk expression. This is significant in that metagenomic studies show that increased fecal Proteobacteria (gram-negative) and a decline in firmicutes (gram-positive) are characteristic of infants who develop necrotizing enterocolitis (NEC). Also, altered and decreased microbial diversity following antibiotic therapy is associated with a later onset of sepsis and NEC.

The value of bovine lactoferrin supplementation was shown in a prospective, multicenter, double-blind trial of lactoferrin alone or combined with the probiotic *Lactobacillus rhamnosus* GG (LGG) to enhance lactoferrin activity and reduce the incidence of a first episode of late-onset sepsis in very low birth weight (VLBW) neonates vs. placebo (P=0.001). Greatest efficacy occurred infants less than 1000g. The decrease occurred for both bacterial and fungal sepsis. There were no cases of NEC greater than stage 2 among 151 patients treated with bovine lactoferrin + LGG vs. control (10/168), and no adverse effects or intolerance to treatment were reported. LGG supplementation offered no added benefit over lactoferrin alone.

Human Recombinant Lactoferrin in VLBW Infants

Based on these and other data, it was hypothesized that enteral administration of human recombinant lactoferrin during a period of limited enteral feeding might reduce healthcare-associated late-onset sepsis in VLBW infants, and that these infants would tend toward a more commensal intestinal microbiome.

Accordingly, a multicenter, randomized, placebo-controlled trial was performed using a man-made (recombinant) form of a naturally occurring human protein — investigational talactoferrin alfa* 150 mg/kg (TLF) in phosphate buffered saline (also used as placebo) was administered via nasogastric tube every 12 hours from day 0 to 28 of life. Dosing was based on the

* Talactoferrin is a man-made (recombinant) form of a naturally occurring human protein that is structurally and functionally identical to native human lactoferrin and FDA-approved for trials in humans.
amount of lactoferrin an infant would receive with full enteral feeds of breast milk. Stools were collected on day 21 of life for 24 hours and DNA extracted using standard techniques with rRNA gene amplification, sequencing and microbiome determination.

The primary endpoints of this study included reductions in bacteremia, pneumonia, urinary tract infection, meningitis and NEC. Secondary endpoints included a reduction in “sepsis syndrome”, “inflammatory-response syndrome”, or “NEC scares” and outcomes of other clinical diseases.

Inclusion criteria included birth weight between 750 and 1500g, informed consent from the parents/legal guardian, and entry by 24 hours of age. Exclusion criteria included documented maternal or neonatal infection at birth, birth depression (cord or initial pH <7.0; Apgar score of ≤3), a major birth defect or malformation syndrome, chromosomal or inherited disorder, proven immunodeficiency, history of illicit substance use, lack of parental consent, refusal by attending neonatologist, or the discretion of the investigator.

Conclusions
The study is now completed and results will be forthcoming. Results supporting the role of lactoferrin enteral administration during limited enteral feeding should lead to additional research to establish its value in NICU clinical practice.

References
Section 3: Clinical Application—Meeting the Challenge of Human Milk for Premature Infants

A New Standard for Quality and Safety in Human Milk Collection and Processing

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The Prolacta quality control manufacturing process is guided by FDA-compliant quality systems.

Human milk banking and plasma collection and processing share many of the same promises and similar risks. The plasma industry has dealt with these every changing risks by continuously innovating to stay ahead of the risk curve. By comparison, management of risk in milk banking has been stagnant for some time now. As the milk banking industry grows rapidly, it must adopt a preventative risk mitigation strategy like the plasma industry.

The FDA does not question the benefits of direct mother/child breastfeeding for almost all babies. However, concerns have been raised that human milk from other sources, including banked milk, might pose greater potential for risk; processing may lessen some of the benefits. Also, concerns exist regarding human milk obtained from sources other than an infant’s own mother, particularly risks associated with transmission of viral infections, chemical contamination and bacterial contamination.²

As a pioneer in standardized human milk-based nutritional products for premature infants in the neonatal/pediatric intensive care unit (N/PICU), Prolacta Bioscience, Inc. (Prolacta) believes it is important to deal with these issues proactively. It is best for everyone (healthcare professionals and patients) that regulatory approaches to risk mitigation be promulgated before any untoward events occur. To this end, this presentation presents what Prolacta has learned and applied to the collection, processing, storage and distribution of bovine-free, human milk products.

Is Milk Safe Enough?
Most people know that smoking causes cancer, heart disease and other major health problems. Smoking during pregnancy causes additional health problems, including premature birth, certain birth defects and infant death.² Yet, tobacco use among pregnant women—whom one might assume should know better—is common (Figure 1)³ and raises the question of the pervasiveness of other drug use among breast-feeding women.

Figure 1. Tobacco use among 251 breastfeeding women after 8 and 24 weeks postpartum.³

Typically, breast milk donors are asked about drug use in the questionnaire, but the milk is not screened. However, since the beginning of 2013, screening by Prolacta has identified 11 breast milk donors as positive for cotinine (metabolite of nicotine). Although a small proportion of all donors screened, it represents a large volume—7775 ounces—of milk disqualified for use. It is apparent that simply asking donors about their use of tobacco products (or taking a social and medical history) does not ensure against contaminated milk. Accordingly, we decided that drug screening is needed, and our results (e.g., cotinine) validate that strategy.
Risks Associated With Human Milk From Sources Other Than the Baby’s Mother

The FDA recommends that the choice of baby human milk from sources other than the baby’s mother should be made in consultation with the baby’s healthcare provider. In addition, suspect sources of breast milk, specifically breast milk acquired directly from individuals or through the internet, should be avoided. In these situations, the donor is unlikely to have been adequately screened for infectious disease or contamination risk, and there is no guarantee that the human milk was collected, processed, tested and stored in a way that reduces possible safety risks to the baby.4

Other examples of common errors committed inadvertently by people trying to act professionally and carefully include comingling of containers of breast milk from different mothers stored in the NICU. Comingling of milk might also occur when neighbors share a freezer until one of them can replace their broken refrigerator/freezer.

We should expect that even when donors are doing their best to follow milk donor requirements, mix-ups and errors occur. The milk banking industry needs to proactively look for ways to detect and eliminate mix-ups and errors at the donor level. This includes the examples discussed above and DNA matching. Good intentions are not enough.

Safeguarding the Quality of Human Breast Milk

Breast milk donations to Prolacta follow a rigorous screening process based on the blood-banking model (Table 1). Mothers meeting all criteria are qualified as breast milk donors for four months, and must repeat the process to continue donating beyond then.

Table 1. Safety Procedures for Potential Donors of Breast Milk Used Exclusively by Prolacta Bioscience, Inc.

<table>
<thead>
<tr>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor is screened using a medical history survey, entered into the</td>
</tr>
<tr>
<td>Prolacta secure database and assigned a donor number</td>
</tr>
<tr>
<td>Potential donor obtains written approval from her physician and her</td>
</tr>
<tr>
<td>baby’s pediatrician</td>
</tr>
<tr>
<td>Donor documents that the freezer temperature is cold enough to store</td>
</tr>
<tr>
<td>human milk</td>
</tr>
<tr>
<td>DNA cheek swab is conducted along with blood tests for infectious</td>
</tr>
<tr>
<td>agents including HIV 1&amp;2, HTLV I&amp;II, HBV, HCV and syphilis</td>
</tr>
</tbody>
</table>

HIV = human immunodeficiency virus; HTLV = human T-lymphotrophic virus; HBV = hepatitis B virus; HCV = hepatitis C virus.

The commitment by Prolacta to advancing the science of human milk has led to building a one-of-a-kind, state-of-the-art manufacturing facility where the most sophisticated and innovative processes, pasteurization and filling methods ensure the highest possible level of product safety and quality. This includes final testing for microbiological and viral contamination. Viruses are detected using polymerase chain reaction — a method that detects as little as one copy of a virus in a sample by amplifying a short sequence of the viral DNA (or RNA) to create many copies.

FDA-Compliant Quality Systems

The entire Prolacta quality control manufacturing process is guided by FDA-compliant quality systems that include maintaining standard operating procedures, staff training, documentation and validation, and compliance and nonconformance management. These procedures exist primarily to protect our consumers by ensuring safe and high-quality products.

Conclusions

Milk banking is often not viewed as what it really is: manufacturing performed by people. Yet, humans make mistakes, even in the most controlled circumstances (e.g., commercial pilots). The drug/biologics manufacturing industry follows strict Good Manufacturing Practices (GMPs) to mitigate the risk of errors; and the milk banking industry must adopt these same GMPs to ensure a safe, consistent product for these fragile babies.

By following strict manufacturing quality control, Prolacta minimizes risk and provides human milk-based nutritional products that help ensure that infants get the additional nutrients they need to grow and thrive. What can the neonatologist do? Neonatologists can be advocates for the premature infant; demand continuous improvement in safety; and audit suppliers and demand proper regulation of human milk banking.

References


100% Human Milk Diet: The Lucile Packard Children’s Hospital Experience

William Rhine, MD
Medical Director, Neonatal ICU
Lucile Packard Children’s Hospital
Professor of Pediatrics (Neonatology)
Stanford School of Medicine
Palo Alto, California

A standardized, consensus-based approach to providing optimal nutrition, using human milk for VLBW infants has been associated with improved growth velocity and reduced NEC at Lucile Packard Children’s Hospital.

The benefits of breastfeeding are extensive (Table 1), and data suggest there are dose–response relationships between the duration of breastfeeding and many of its protective outcomes. The objective of this study was to improve outcomes for our infants at Lucile Packard Children’s Hospital (LPCH) through the use of a 100% human milk diet.

Resources and Commitment
Initiation and adherence to a 100% human milk diet requires a multidisciplinary effort, including a commitment from the mothers. Education starts prenatally by obstetricians, with continued emphasis during labor and delivery by obstetric and neonatal services. Postpartum support continues with encouragement by neonatal intensive care unit (NICU) nurses, physicians and dieticians who answer questions and support the nursing mother. Lactation consultants play a central role throughout this process.

Although education and ongoing support are important, the greatest success is achieved in a supportive physical environment with the availability of appropriate equipment and use of proper technique. For example, the best way to optimize milk production and increase caloric content is with hand expression combined with the use of a breast pump.

Eleven NICUs in the California Perinatal Quality of Care Collaborative participated in an Institute for Healthcare Improvement-style collaborative to increase NICU breast milk feeding rates. The results showed that a commitment to bundling of practices to improve breast milk availability was associated with a relative 13% improvement in the percent of very low birth weight (VLBW) infants being sent home on breast milk. Mothers who apply these techniques are able, in many cases, to meet and exceed the nutritional needs of their babies.

Table 1. Benefits (reduced risk) associated with breastfeeding and the use of human milk.

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term benefits</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>-60%</td>
</tr>
<tr>
<td>Lower respiratory infection</td>
<td>-72% to -77%</td>
</tr>
<tr>
<td>Respiratory syncytial virus bronchiolitis</td>
<td>-74%</td>
</tr>
<tr>
<td>Sudden infant death syndrome</td>
<td>-36%</td>
</tr>
<tr>
<td>Otitis media</td>
<td>-23% to -50%</td>
</tr>
<tr>
<td>Recurrent otitis media</td>
<td>-77%</td>
</tr>
<tr>
<td>Allergies: atopic dermatitis</td>
<td>-27% to -42%</td>
</tr>
<tr>
<td>Gastrointestinal: gastroenteritis</td>
<td>-64%</td>
</tr>
<tr>
<td>Necrotizing enterocolitis (NEC)</td>
<td>7.2% [formula] to 1.6% [human milk] in infants &lt;1850g</td>
</tr>
<tr>
<td>Long-term benefits</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
</tr>
<tr>
<td>Acute myelogenous leukemia</td>
<td>-15%</td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>-20%</td>
</tr>
<tr>
<td>Cardiovascular: blood pressure</td>
<td>3.2 mmHg lower</td>
</tr>
<tr>
<td>Neurodevelopmental outcomes</td>
<td></td>
</tr>
<tr>
<td>Improved IQ scores and teacher ratings</td>
<td></td>
</tr>
<tr>
<td>Maternal benefits: reduction</td>
<td></td>
</tr>
<tr>
<td>in diabetes, hypertension, breast</td>
<td></td>
</tr>
<tr>
<td>and ovarian cancer</td>
<td></td>
</tr>
</tbody>
</table>
For mothers who are still unable to produce sufficient breast milk, alternative sources of human breast milk include banked breast milk in conjunction with a local Human Milk Bank Association of North America (HMBANA) milk bank and commercial sources such as Prolacta Bioscience, Inc. Using these sources meets the nutritional needs of the infant and reinforces the commitment to the benefits of human milk.

**Optimizing Nutrition of VLBW Infants at LPCH**

Table 2 lists strategies to optimize nutrition of VLBW infants at LPCH. Over 90% of the mothers of our VLBW infants provide breast milk; if mother’s milk is not available, banked breast milk is strongly recommended. The use of human milk-based fortifier (Prolacta) supports our commitment to using human milk as the optimal enteral nutrition for these patients, resulting in 85% of inborn VLBW infants being discharged on at least some breast milk (top 10% of VON [Vermont Oxford Network] NICUs).

**Table 2. Strategies to optimize nutrition of VLBW infants at LPCH.**

| • Encourage use of human milk |
| • Early total parenteral nutrition (TPN) |
| • Gastrointestinal priming/trophic feeds |
| • Defined feeding advance schedule |
| • Standardized fortification |
| • Consensus around residuals and feeding intolerance |

Efforts are made to optimize the postnatal transition from total parenteral nutrition (TPN) in VLBW infants. Initial protein administration is 2g advanced up to 3.5 to 4 g/kg/day. Initial lipid administration starts at 1g advanced to 3 g/kg/day. The use of Colostrum administered buccally is encouraged in all babies, which reinforces the mother’s commitment to provide milk.

The feeding advancement pathway starts with a small volume of mother’s breast milk (MBM) as available. This pathway was developed by consensus and is embedded into our computerized order set. Re-initiation of the pathway after adjusting for feeding intolerance is individualized based on the patient’s clinical condition. Importantly, the order set no longer lists “formula” as the default alternative to MBM.

In past 3 years, we have used Prolacta fortifier up to 1500g/34 weeks gestational age, then transitioned to other liquid fortifiers. Typically, we use Prolacta 24 Cal/oz (Prolact+4®) at up to 170 mL/kg/day. If faced with inadequate growth, this is increased to 26 Cal/oz (Prolact+6®). Babies on formula feeds have fortification by increasing formula caloric concentration.

We avoid powdered fortifier products and thickeners. The use of residuals to guide feeding is nonspecific. Therefore, at LPCH emphasis is on the whole patient evaluation.

**Clinical Response to Optimized Nutrition of VLBW Infants at LPCH**

The benefits associated with the nutrition strategies implemented at LPCH for VLBW infants over 3 years are illustrated in Figures 1 and 2. Using VON as a basis for comparison, there has been improved inborn growth velocity (g/kg/day) and a decreasing rate of necrotizing enterocolitis (NEC).

**Figure 1. Improved inborn growth velocity (g/kg/day): LPCH vs. VON over 3 years of a multidisciplinary strategy to improve nutrition of VLBW in infants using 100% human milk.**

**Figure 2. Decreasing rate of NEC: LPCH vs. VON over 3 years of a multidisciplinary strategy to improve nutrition of VLBW in infants using 100% human milk.**

LPCH = Lucile Packard Children’s Hospital; NEC = necrotizing enterocolitis; VON = Vermont Oxford Network; VLBW = very low birth weight.
Conclusions
These results support the importance of a multidisciplinary commitment to achieve our primary goal of improving nutritional support for our NICU patients. In addition, success with breast milk benefited by maximizing its availability and fortification with human milk-based fortifier (Prolacta) for VLBW infants. This approach has been associated with improved growth velocity and reduced NEC, as well as higher rates of VLBW infants going home on breast milk.

References

DoMINO and OptiMoM

Deborah O’Connor, RD, PhD
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Professor, Department of Nutritional Sciences
University of Toronto
Toronto, Ontario, Canada

A grass roots group of health clinicians were interested in establishing a donor human milk bank in Ontario in order to decrease the risk of NEC in VLBW infants. The group was also interested in exploring the impact of using donor human milk on long-term neurodevelopment.

The Donor Milk for Improved Neurodevelopmental Outcomes (DoMINO) randomized control trial and the Optimizing Mothers’ Milk for Preterm Infants (OptiMoM) program were developed as a mechanism to establish the use of pasteurized donor human milk in Ontario, Canada for necrotizing enterocolitis (NEC) prevention and to evaluate the impact of its use on other health outcomes with special emphasis on measuring neurodevelopment in the infants as a function of dosing.

In addition to the investigation of the impact of feeding type (own mother’s milk, donor human milk, infant formula) on mortality and morbidity, our team is interested in how human milk needs to be modified by the addition of extra nutrients to meet the unique and elevated nutritional and growth requirements of the preterm infant. Data from our group show as much as a 10-point advantage in cognitive scores among very low birth weight (VLBW) infants aged 18 to 24 months corrected age that follow a sustained growth curve compared to VLBW infants that follow a decelerated rate of growth, even after statistical adjustment for major morbidity (Table 1).¹

We also know from our own work that VLBW infants fed own mother’s milk have superior neurocognitive development.² This is thought due, at least in part, to the fact that human milk is better tolerated allowing for more rapid transition from parenteral to enteral nutrition and that human milk offers a favorable bioactive composition. Although knowledge of the gut microbiota in VLBW infants is limited, data suggest that the microbiota is influenced by diet and the gut–brain axis and microbiome–host interaction contribute to brain development and behavior and influence the nervous system.³

These findings are supported by other reports. Dr. Betty Vohr and colleagues for the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network⁴ showed in a sample of more than 1000 extremely low birth weight infants that for every 10 mL/kg/day increase in breast milk ingestion, their Mental Development Index increased by 0.53 points, their Psychomotor Development Index increased by 0.63 points and their Behavior Rating Scale percentile score increased by 0.82 points at 18 months corrected age. These benefits persisted to
30 months, where for every 10 mL/kg/day increase in breast milk, the Mental Developmental Index increased by 0.59 points, the Psychomotor Developmental Index by 0.56 points and the total behavior percentile score by 0.99 points.\(^5\)

Despite data in the literature suggesting that the use of pasteurized donor human milk would help reduce the risk of NEC among VLBW infants, until recently infants in most neonatal intensive care units (NICUs) in Ontario received infant formula as a supplement to mother’s own milk when the latter was unavailable.\(^5,7\) General awareness of donor milk and its beneficial attributes was low, even among healthcare professionals. While data do not exist to quantify, informal milk sharing occurred. There was only one milk bank in Canada, which was located in Vancouver. Clearly this was insufficient to meet the needs of Ontario.

**DoMINO Project**

Our goal for Ontario was to establish the use of a donor human milk program in order to reduce the risk of NEC among VLBW infants and to evaluate the impact of its use on other health outcomes with special emphasis on measuring neurodevelopment. We believed that bringing in donor milk to a large consortium of NICUs as part of a research project would facilitate this effort. DoMINO is funded by a competitive operating grant from the Canadian Institutes of Health Research (CIHR).

DoMINO was designed to study VLBW infants’ response to pasteurized donor human milk vs. formula during initial hospitalization when a mother’s own milk is unavailable. Infants are randomized within 4 days of birth, and they continued in the study after transfer to a participating Level II hospital. A consortium of NICUs from the greater Toronto and Hamilton areas came together to work on this project.

Our primary research hypothesis is that pasteurized donor human milk will be associated with improved neurocognitive development at 18 to 24 months corrected age. Second, we anticipate that the use of donor human milk will support growth, and through preferential development of gut microbial community composition will reduce neonatal mortality and morbidity. We also hope to demonstrate that this nutritional strategy is cost effective from a societal perspective.

**DoMINO Interim Results**

The Rogers Hixon Ontario Human Milk Bank is established and dispensing milk. Its goal is to dispense milk to all babies born weighing <1500g in Ontario who need it for up to 4 weeks.

Enrollment in DoMINO is complete, with 363 infants randomized to treatment. After accounting for withdrawals and deaths, there are 316 participants. Among the 840 mothers approached to participate, many of those who declined did so because they did not want to use donor milk.

Baseline demographics are comparable to the Canadian Neonatal Network. Average weight (±SD) is 981±266g and the average gestational age at birth was 27.6±2.5 weeks. There has been a 10% in-hospital mortality rate, 33% of babies diagnosed with chronic lung disease, 30% with sepsis and a 3% rate of NEC. More results will be forthcoming as data analysis progresses.

**OptiMoM Program**

OptiMoM was recently funded for 5 years through a CIHR Programmatic Grant in Foods and Health. The OptiMoM team is composed of a unique interdisciplinary group of Canadian researchers, clinicians and policy makers who have assembled to evaluate and translate into policy very promising nutritional strategies that have a high likelihood of impacting the survival as well as short- and long-term health outcomes of VLBW infants. A consortium of six tertiary and 16 affiliated community NICUs from the provinces of Nova Scotia, Ontario and British Columbia representing ~40% of all Canadian VLBW infants born annually is in place. Evaluation of strategies will occur simultaneously across inter-related domains known to be affected by nutrition (neurodevelopment; gut health; growth and body composition).

The OptiMoM program provides funding for the follow-up of babies enrolled in DoMINO at 5-6 years of age and two additional randomized control trials. The key research hypotheses of these projects are listed in Table 2.

---

**Table 1. Pattern of weight-for-age gain between birth and 18 to 24 months corrected age on the World Health Organization (WHO) growth charts and developmental outcome at 18–24 months corrected age.\(^7\)**

<table>
<thead>
<tr>
<th>Outcome (WHO)</th>
<th>Bayley Scales of Infant and Toddler Scores (mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Decelerated growth</td>
</tr>
<tr>
<td>Cognitive</td>
<td>96.2±13.8&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Language</td>
<td>91.0±12.5&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Motor</td>
<td>100.0±5.4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*Statistically controlled for demographic and clinical confounders; unlike superscript letters within each row denote a statistically significant difference (P<0.05). Reproduced with permission of the author.*
Table 2. Objectives for OptiMoM-funded DoMINO follow-up studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary Objective</th>
<th>Secondary Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1: Impact of feeding donor milk as a supplement to mother’s milk on the growth and development of VLBW infants at 5-6 years (school readiness)</td>
<td>Does donor milk, vs. preterm formula, as a supplement to own mother’s milk for the first 90 days of life or hospital discharge improve cognitive development of VLBW infants at 5-6 years of age?</td>
<td>(i) Improve other facets of cognitive development including language development, performance IQ and processing speed (ii) Reduce likelihood of overweight/obesity (iii) Improve measures of brain structure and function?</td>
</tr>
<tr>
<td>Study 2: Effectiveness of human milk-based vs. bovine-based fortifiers</td>
<td>Does adding a human milk-based nutrient fortifier vs. bovine protein-based nutrient fortifier to human milk fed to VLBW infants during initial hospitalization improve feeding tolerance?</td>
<td>(i) Support growth (ii) Promote a favorable gut microbiome and reduce gut inflammation (iii) Reduce neonatal mortality and morbidity?</td>
</tr>
<tr>
<td>Study 3: Effectiveness of increasing protein intake of VLBW infants</td>
<td>Does adding 1.0 g/kg/day protein to human milk (own mother’s milk, donor milk) to target a total protein intake of 4.5-5 vs. 3.5 g/kg/day during initial hospitalization improve cognitive outcomes of VLBW infants at 18-24 months corrected age?</td>
<td>(i) Improve language and motor development at 18-24 months corrected age (ii) Enhance brain structure, metabolism and connectivity between cognitive brain processing regions (iii) Promote growth (iv) Increase lean body mass (v) Reduce neonatal mortality and morbidity milk?</td>
</tr>
</tbody>
</table>

Conclusions

The importance of own mother’s milk to facilitate growth and development of infants, including the preterm infants is undisputed. Through the DoMINO randomized control trial and the OptiMoM program of research, we have the unique opportunity of exploring and evaluating promising strategies to facilitate the use of human milk for the vulnerable preterm infant. The DoMINO project has already achieved two important goals: to raise awareness of the benefits of human breast milk and to facilitate the establishment of a human milk bank to serve the hospitals in Ontario.

References

A favorable group decision at Thomas Jefferson University Hospital was reached only after agreeing that breastfeeding rates would not be compromised. The role of donor milk was to serve as a bridge, not a substitute.

Recognition of the importance of human breast milk is growing. In 2009, the United Nations Children’s Fund (UNICEF) and the World Health Organization (WHO) called for more widespread application of the baby-friendly hospital initiative, and pointed to the neonatal intensive care unit (NICU) as an area ripe for expansion. Now, the Joint Commission has announced that the perinatal care core measure set will become mandatory for all hospitals with 1100 or more births per year, effective January 1, 2014. They will record the number of healthy term infants without a contraindication to breastfeeding that are exclusively breast milk-fed. In addition, Baby-Friendly USA is developing a baby-friendly initiative for NICUs.

What follows is our experience in conception, logistics and operation of a human donor milk service at Nemours duPont Pediatrics at Thomas Jefferson University Hospital (TJUH), in Philadelphia. Nemours is a 40-bed level IIIC NICU, with approximately 600 admissions per year including 50 to 60 very low birth weight (VLBW) infants. The pediatric unit is part of a large urban academic hospital system that provides predominantly adult-centered services in an urban setting.

Changing the Culture
Prior to the human donor milk service, feeding practices at TJUH centered on using bovine milk-based fortifier. Figure 1 shows the level of knowledge and comfort among our staff members on the use of donor breast milk. All nurses knew about donor breast milk, and most were comfortable explaining and recommending it to mothers. Only 41% of nurses, however, stated that they were comfortable providing donor breast milk to an infant in the NICU, although 73% would be comfortable donating their breast milk were they a lactating mother. Among parents surveyed, 48% knew about donor breast milk and 23% would provide it to their infants; 29% were willing to donate their milk if they had a surplus.

Changing the Culture
Feeding practices started to change in 2010 in response to an evidence-based educational program targeted to all stakeholders and their specific concerns. This included the department of pediatrics and division of neonatology, nutrition, legal council, infection control team and parents. Emphasis was placed on safety and the nutritional and biological quality of milk from a human milk bank, quality control measures, and the medical and neurodevelopmental advantages of human milk.

Hospital administration had to be convinced of the comparative benefits of alternatives sources. Prolacta Bioscience products provided advantages in consistency, infection control and availability, although those from the Human Milk Bank Association of North America (HMBANA) were less expensive (Table 1). The program also had to satisfy the ten steps to successful breastfeeding in accordance with the baby-friendly initiative.
Logistics is a major challenge in establishing a donor breast milk service. Issues include selecting the location and space allotment at the primary site, ownership of the services (i.e., pharmacy or nutrition), budgets and staffing, and future impact of expansion of the service. It is also necessary to develop policies and procedures, a marketing plan, formal staff training and implementation.

A favorable group decision at TJUH was reached only after agreeing that breastfeeding rates were not to be compromised. The role of donor milk was to serve as a bridge, not a substitute.

Use of Prolacta Fortifier

Prolacta fortifier was introduced in a stepwise manner, primarily due to budgetary constraints. Initiated in 2011, it was reserved for infants weighing less than 1000g and introduced after they tolerated 120 mL/kg/day of enteral feeds. A feeding protocol implemented in 2012 facilitated earlier establishment of enteral feeds and feeding advancement. The protocol was revised in July 2013 to permit the use of Prolacta fortifier when the infant tolerated 40 mL/kg/day of enteral feeds and expanded to include infants weighing less than 1250g.

Figure 2 shows the change in occurrence of necrotizing enterocolitis (NEC) and reduced feeding intolerance associated with using Prolacta fortifier.

Conclusions

The environment at Nemours duPont Pediatrics is similar to many NICUs in the US, in that it is a small part of a much larger institution. Agreement on the use of donor human milk was based on the results of evidence-based research and recognition that success required addressing the concerns of all stakeholders. We recognize today that this is only part of the challenge. Ongoing success of the donor human milk program requires constant monitoring and education to ensure that we continue to meet the needs of NICU patients. This must be accomplished in a way that does not compromise breastfeeding rates and complements baby-friendly initiatives in the nursery and pediatrics department.

It is hoped that our experience will assist others in expanding the use of human breast milk to improve the care of our most vulnerable patients and meet the emerging Joint Commission guidelines.

<table>
<thead>
<tr>
<th>Table 1. Comparison of sources of human donor milk by Nemours duPont Pediatrics at Thomas Jefferson University Hospital.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HMBANA</strong></td>
</tr>
<tr>
<td><strong>Consistency of product</strong></td>
</tr>
<tr>
<td><strong>Infection control</strong></td>
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<tr>
<td></td>
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<tr>
<td><strong>Availability</strong></td>
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<td></td>
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<tr>
<td><strong>Cost</strong></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

HMBANA = Human Milk Bank Association of North America.
References


Closing Remarks

William Rhine, MD
Medical Director, Neonatal ICU
Lucile Packard Children’s Hospital
Professor of Pediatrics (Neonatology)
Stanford School of Medicine
Palo Alto, California

Dr. German and I wish to thank Prolacta for sponsoring the 1st Annual International Conference on Human Milk Science and Innovation. The presentations informed and updated our understanding of human milk research and options available to provide nutritional support for very low birth weight (VLBW) infants.

Human milk is the optimal source of human nutrition. It provides elements that benefit the neonate, including oligosaccharides, protein and immune factors. The impact of pasteurization is less studied in VLBW infants, but most bioactive components of pasteurized milk are maintained, albeit in some cases at lower concentrations.

Clinical research documents that aggressive use of a 100% human milk diet supports better growth in premature infants, with weight gain exceeding targeted growth standards. Infants who receive cream supplement added to fortified human milk improved length velocity from birth compared to controls; and lactoferrin enteral administration during limited enteral feeding may reduce healthcare-associated late onset sepsis.

Application of clinical research to clinical practice requires a significant commitment from industry, regulators, accreditation organizations and healthcare providers, as well as parents. The FDA supports the benefits of breastfeeding for almost all babies. However, concerns about the safety and composition of human milk from other sources, including banked milk, must be addressed. Prolacta is taking a proactive approach to addressing these issues, and we acknowledge their commitment to advancing the science of human milk nutrition, as evidenced by their new world-class facility in southern California. I trust that what we heard during this conference and reported in this white paper report will inspire collaboration among research institutions worldwide to advance nutritional options for premature infants—who are such precious but vulnerable members of our society.