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Missed Opportunities: The Cost of Suboptimal Breast Milk Feeding in the Neonatal Intensive Care Unit

Nowhere in modern medicine does the decision about what to feed a patient have such immediate impact on short-term mortality and long-term morbidity as in the extremely premature infant. Necrotizing enterocolitis (NEC) is a common and devastating complication of very preterm birth, and several studies have demonstrated a decrease in the incidence of NEC with the feeding of mother's milk. Although many of the morbidities associated with extreme premature birth have decreased during the past 2 decades, the incidence of NEC has remained fairly stable.[1] For the extremely premature infant who survives beyond the first 2 weeks of life, NEC is the most common cause of death until 34 weeks' corrected gestational age. For premature infants who survive an episode of NEC, the risks of poor growth, malabsorption, short-bowel syndrome, and neurodevelopmental delays are significant.

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Human milk is a marvelously complex cocktail of macronutrients, micronutrients, bioactive molecules, and cellular components that maintains a delicate balance to nourish and protect 2 fragile populations (infants and their intestinal microbial communities) without excessive cost to the mother. Whether one sees the intricacies of human milk and the commensal microbes that use human milk components as a food source as a powerful example of coevolution of multiple species or sees the hand of a creator guiding this coevolution, it is difficult to study human milk without awe bordering on reverence! Human milk has many components that likely contribute to the prevention of NEC; 3 recent human milk discoveries are of particular relevance to premature infants and NEC.

Human Milk Oligosaccharides (HMOs)

More than 200 structures of HMOs have been identified in human milk, with wide variation between women and within a given woman over time. These complex carbohydrates consist of a lactose core extended with up to 5 types of monosaccharides (glucose, galactose, N-acetylglucosamine, fucose, and sialic acid) in a variety of linkage patterns. Although HMOs are highly abundant (similar in volume to human milk protein), they are not digestible by the human intestinal tract. The compelling evolutionary question is, of course, why is the mother expending tremendous energy and resources to craft these complex sugars that have no nutritive

HMO	Human milk oligosaccharide
HMP	Human milk peptide
Lf	Lactoferrin
NEC	Necrotizing enterocolitis

Funding provided by the National Institutes of Health (R01-HD059127 and UL1 TR000002) and the Children's Miracle Network. The author declares no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2016.05.016

value for her infant? To add to the puzzle, HMOs are a food source for just 2 of the hundreds of bacterial genera that form the intestinal microbiota: *Bacteroides* and *Bifidobacterium*. These 2 observations, that lactating women developed the capacity to produce HMOs and a select group of gut microbes concurrently evolved the enzymes necessary to transport and digest HMOs, suggest that mothers produce HMOs to shape the intestinal microbiota of their babies.[2] In developing countries, bifidobacteria are the predominant component of the breast-fed infant fecal microbiota,[3] whereas in developed countries this predominance is lost, likely as the result of changes in diet and hygiene that have altered the maternal microbiota from that shaped by evolution.

Intestinal dysbiosis early in life appears to underlie not only NEC in premature infants, but a host of pediatric and adult diseases, including metabolic syndrome, obesity, and allergic and atopic disease. If provision of a food source for desirable commensal organisms were the sole mechanism by which HMOs prevent NEC, one would expect large numbers of bifidobacteria and/or *Bacteroides* in the feces of human milk-fed premature infants and yet this is not the case. Several HMOs have structural similarity to host surface glycans and thus serve as decoys to bind intestinal bacteria and viruses, which are thus unable to bind to the host mucosa. In addition, HMOs have antimicrobial and immunomodulatory effects[4,5] and demonstrate heterogeneity in absorption from the gastrointestinal tract and in their influence on the intestinal microbiota.[6] Thus, the protective effect of HMOs in premature infants may have more to do with suppression of potential pathogens and/or immune signaling than increased colonization with commensals.

Lactoferrin (Lf)

Lf is a complex glycoprotein that is abundant in human milk and provides a variety of protective activities, including iron hemostasis, antimicrobial activity, immunomodulation, and anti-inflammatory and antioxidant properties. In addition to milk, Lf is found in most mucosal secretions and in granulocytes and accumulates in the liver, kidneys, spleen, and brain. Digestion of Lf in the intestinal lumen is complex and releases bioactive peptides such as lactoferricin. Lf inhibits the growth of *Escherichia coli* and *Salmonella* sp but stimulates the growth of bifidobacteria and thus also shapes the intestinal microbiota.[7] Administration of bovine Lf to premature infants appears to be protective against NEC.[8,9]

Human Milk Peptides (HMPs)

Human milk contains hundreds of peptides derived from human milk proteins by proteases in the mammary gland and in the stomach. Many of these peptides are biologically active with antimicrobial and immunomodulatory properties. For instance, groups of HMPs are able to kill both *E coli* and *Staphylococcus aureus*.[10] A comparison of gastric aspirates from premature vs term infants demonstrated increased numbers of HMPs in the premature infants, suggesting a possible protective effect (ie, increased human milk protein degradation in the immature mammary gland).[11]

In this volume of *The Journal*, Colaizy et al[12] present a thoughtful analysis of a large cohort of premature infants, bridging the 20th and 21st centuries for whom detailed information about intake of mother's own milk is available. In this cohort, as in others,[13] the administration of human milk is protective against NEC. The detailed data regarding nutritional intake for these infants allowed computation of the potential savings in dollars and lives of increased provision of mother's milk.

Although one may argue with many of the assumptions (eg, the feasibility of the proposed target of >90% of extremely premature infants receiving >98% human milk in a time when maternal drug use is common and rising, the accuracy of the estimate of current levels of human milk provision, and the relatively small number of infants in the original cohort that make up the "ideal" group), the conclusions of the exercise only vary in magnitude not in direction.[14] Regardless of how one tweaks the assumptions, the only possible conclusions are profound. It takes significant time, energy, and resources for the mother of an extremely premature infant to provide an adequate supply of milk for her infant, and the costs (time, energy, and resources) of supporting this mother in her efforts are very small compared with the costs of suboptimal breast milk provision and less than the costs of premature infant formula or donor human milk.

Interventions to facilitate the provision of human milk by mothers of premature infants have been well-described and include collaboration among all stakeholders in the hospital,[15] consistency among staff in information provided about human milk,[16] assistance in initiating lactation and maintaining an adequate milk supply,[17,18] and encouragement and education from lactation experts and breastfeeding peer counselors.[19]

On a larger scale, one could make a compelling argument that the dismal experiment of the 1960s and 1970s wherein formula feeding of healthy term infants was believed to be equivalent to human milk feeding has contributed to astronomical costs to society, including lost intelligence, loss (perhaps permanent) of the intestinal microbiota shaped by millions of years of evolution, and the resultant increases in a broad array of chronic disease processes. In the neonatal intensive care unit and beyond, human milk nutrition may be one of the safest and most cost effective interventions to promote childhood and adult health. ■

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A Pediatric Perspective on Value-Based Insurance Design

"When I approach a child, he inspires in me two sentiments; tenderness for what he (she) is, and respect for what he (she) may become." This quote by Louis Pasteur expresses the aspirations of pediatricians in their care for children. Attending to the child's immediate health needs while ensuring preventive services, anticipatory guidance, and screening for emerging longitudinal risk factors are fundamental functions of pediatric primary care. Although injury remains the leading cause of childhood mortality,[1] obesity, developmental disabilities, sequelae of premature birth, asthma, and mental and behavioral conditions account for an increasing portion of childhood morbidity.[2,3] In addition, the recognition that risk factors for adult chronic disease emerge during childhood, as highlighted by the impact of adverse childhood experiences, gives meaning to an approach to pediatric health care that is comprehensive and longitudinal.[4] As the focus on improving population health becomes more acute, the need to establish the foundations of health for every child becomes even more important.

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Pediatric primary care is the platform from which childhood health care, preventive services, and anticipatory guidance are delivered, and the core of the pediatric platform is the medical home. The American Academy of Pediatrics developed the medical home as a model of delivering primary care that is accessible, continuous, comprehensive, family-centered, coordinated, compassionate, and culturally effective to every child and adolescent. Medical homes address preventative, acute, and chronic care from birth through transition to adulthood. A medical home facilitates an integrated health system with an interdisciplinary team of patients and families, primary care physicians, specialists and subspecialists, hospitals and health care facilities, public health, and the community.[5]

Comprehensive care in a pediatric primary care medical home has been associated with increased odds of children being read to, improved sleep hygiene, the use of bike helmets, decreased screen time, decreased outpatient and emergency department sick visits, and increased preventive care visits and parent-reported increased child health. Not surprisingly, children without a medical home are more likely to have unmet medical needs.[6-8] The medical home is the recommended standard for provision of high-quality, comprehensive health care for all children, but there are disparities in access to care in a medical home. Children who are Hispanic, black, and from low socioeconomic status are less likely to receive care, whereas children with health insurance are more likely to receive care in a medical home.[6]

A pediatric medical home is a family-centered partnership within a community-based system that provides uninterrupted care with appropriate payment to support and sustain

The views contained in this editorial are expressly those of the author and do not represent any views of the institutes with which the author is associated. The author of this editorial is the Medical Director of the American Academy of Pediatrics Institute for Healthy Childhood Weight, of which Martín-Jose Sepúlveda, MD, is a member of the advisory board.

The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2016.05.062