Mid-Atlantic Mothers' Milk Bank

The Case for Donor Milk Coverage in Pennsylvania

Evidence Based Use in Selected Populations

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Definitions

DRG: Diagnosis-related group. The DRG is a patient classification system that standardizes prospective payment to hospitals and promotes cost containment initiatives. Typically, the DRG payment covers all charges associated with an inpatient stay from admission to discharge. Most hospitals in Pennsylvania are paid through this type of reimbursement system.

HMBANA: The Human Milk Banking Association of North America (hmbana.org). Accrediting body of the 31 non-profit milk banks across the United States and Canada. HMBANA accredited milk banks must strictly follow evidence-based guidelines for donor screening, milk testing, milk processing, and distribution and are subject to frequent inspection.

Milk Bank: Human milk banks collect milk from donors and process, screen, store, and distribute donated milk to meet the specific needs of individuals for whom human milk is prescribed by licensed health care providers. The Pennsylvania Department of Health is responsible for licensing milk banks per the requirements of Act 7 of 2020.

Mother Baby Unit/Nursery: Inpatient unit where mothers and healthy newborns are cared for following delivery until discharge. Also may be referred to as a level I NICU.

NEC: Necrotizing Enterocolitis. An inflammation of the intestines that primary affects infants. Significantly premature infants and those with certain congenital or acquired condition are most at risk. NEC is a common emergency in the NICU setting and a major contributor to mortality and disability in the premature infant population.

NICU: Neonatal Intensive Care Unit. There are 4 levels of NICUs based on the severity of conditions they are able to treat. Level III and IV NICUs have the capability to care for critically ill infants and those born before 32 weeks gestation.

Pasteurization: A food manufacturing process involving the application of mild heat (under 100°C) to inactivate pathogens and extend storage life.

PDHM: Pasteurized Human Milk.

VLBW Infant: Neonate born weight 1500g (3.3 lbs.) or less. VLBW infants are at greater risk for the complications of prematurity.

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Introduction

Human milk optimizes the health and well-being of all infants but is absolutely essential for infants born prematurely or ill. For these medically fragile infants, an all or near all human milk diet provides powerful, unparalleled protection against serious complications that can lead to longer hospitals stays, multiple procedures, readmissions, life-long disability, or even death.

Unfortunately, up to 70% of mothers who have infants in the neonatal intensive care unit (NICU) are unable to provide all of their baby's needs [1], at least initially, despite adequate lactation support and effort. There are several factors that can initially delay copious milk production, cause temporary or long-term supply issues, or even make breastfeeding contraindicated. Examples of such factors include premature birth, cesarean section, medication use, diabetes, drug abuse, obesity, use of fertility treatments, and hypothyroidism.

Mother's milk has unique properties tailored to her own child's needs and is always the best nutrition with rare exceptions. When mother's own milk is unavailable, the use of Pasteurized Donor Human Milk (PDHM) for necessary supplementation is a proven, cost-effective way to improve health outcomes and lower health care costs.

While premature infants and those being cared for in the NICU are the primary recipients of PDHM, other infants require human milk to thrive as well. Outpatient and inpatient infants with acquired or congenital gastrointestinal or cardiac conditions, severe allergies, immunological issues, malabsorption issues, or other circumstances greatly benefit from donor milk too.

Overview of Human Milk Banking

Pasteurized Donor Human Milk (PDHM) refers to milk from carefully screened donors that is pasteurized to inactivate pathogens and tested. Milk banks must be licensed in Pennsylvania to collect or distribute donor milk in the Commonwealth.

The vast majority of research pertaining to the efficacy of donor milk in the United States was done using milk processed by milk banks that are members of the Human Milk Banking Association of North America (HMBANA), which was established in 1985 to accredit non-profit milk banks and provide guidelines for screening, processing, and distribution.[2]

By using evidence-based protocols that employ multiple, overlapping quality control methods, HMBANA accredited milk banks have had an exceptional record of providing safe donor milk to medically fragile infants for over four decades.

There are currently 31 HMBANA accredited non-profit milk banks in North America, each strictly adhering to HMBANA's guidelines and subject to frequent inspection and evaluation. Currently, only a handful of states (including Pennsylvania) regulate milk banks, with most using the HMBANA guidelines as a standard. The FDA requires milk banks to register as Food Manufacturing Services, under the Current Good Manufacturing Practice (CGMP) regulations.

The donors of HMBANA accredited milk banks are unpaid volunteers that must pass a thorough 4-part screening process, which includes a phone interview, the completion of a detailed application packet and medical history, signed statements of health from the healthcare providers of both the prospective donor and her infant, and blood testing for bloodborne pathogens including HIV, HTLV, Syphilis, and Hepatitis B and C. Donors are not compensated in any way, but all costs associated with screening and shipping donated human milk are paid for by the non-profit milk bank. HMBANA strictly prohibits donor remuneration due to significant safety and ethical concerns.

The milk of up to five donors is pooled together to even out nutritional differences and enhance the variety of immunological factors present. After mixing, donated milk is bottled and then pasteurized. All HMBANA milk banks use the Holder Method of Pasteurization (30 minutes at 62.5°C) which inactivates pathogens while maintaining the majority of bioactive components such as Secretory IgA (the main immunological component of human milk), lysozyme, and human milk oligosaccharides (promotes a healthy microbiome).[2-5] HMBANA guidelines do not allow for the retort processing of human milk to create a shelf stable or sterilized product due to a lack of efficacy studies in the NICU population and emerging evidence demonstrating the destruction of the important bioactive components mentioned above along with clinically significant reductions in thiamine content. [6-8]

After pasteurization, a random bottle from each processed batch is sent for bacterial culture testing and batches that show growth of any kind are discarded or used for research. Processed donor milk is frozen until use and is distributed by prescription or hospital order only.

With the exception of donor remuneration, for-profit milk banks licensed in the Commonwealth of Pennsylvania follow similar donor screening and milk processing procedures.

Health Benefits and Improved Outcomes

To maximize both child and maternal health outcomes, the ideal diet for nearly all infants is an exclusive human milk diet for the first six months of life followed by the gradual introduction of solid foods. Fortunately, the vast majority of infants that do not have access to mother's own milk are healthy and able to tolerate commercially available formulas. While the number of infants that have a medical need for PDHM is small, they are a medically fragile population often with complex and significant issues

which put them at risk for serious complications along with growth and development problems. The medical conditions described below include the most frequent needs for PDHM encountered by milk banks and hospitals. This list is not exhaustive as other circumstances could necessitate the use of PDHM based on the specific requirements of individual infants.

Reduction of Morbidity and Mortality in the NICU Setting

A large body of evidence has shown that in the NICU setting, the use of PDHM to achieve an all or near all human milk diet when mother's own milk is unavailable reduces mortality rates, lowers healthcare costs, and shortens hospital stays while increasing rates of exclusive maternal breastfeeding. Specifically, the use of PDHM is associated with increased survival rates and lowered rates of infections, sepsis, retinopathy of prematurity (major cause of blindness in premature infants), bronchopulmonary dysplasia (a serious lung disease), and GI complications.[9,10]

The benefits of human milk extend beyond the inpatient stay with infants receiving all human milk diets in the NICU experiencing fewer hospital readmissions and better overall long-term outcomes.[11]

Due to this ever-growing evidence, the use of PDHM has rapidly become the standard of care in NICUs across the United States. In 2012, as part of its policy statement *Breastfeeding and the Use of Human Milk,* the American Academy of Pediatrics stated "The potent benefits of human milk are such that all preterm infants should receive human milk. Mother's own milk, fresh or frozen, should be the primary diet, and it should be fortified appropriately for the infant born weighing less than 1.5 kg. If mother's own milk is unavailable despite significant lactation support, pasteurized donor milk should be used."[12]

Prematurity

In the United States, one in nine infants are born prematurely, one of the highest rates among developed countries.[13] A full-term pregnancy is 40 weeks and prematurity is defined as a birth occurring at or before 37 weeks of gestation. Premature and very low birth weight (VLBW) infants (those weighing 1.5kg/ 3.3 lbs. or less) are especially vulnerable to complications in the NICU and particularly benefit from the anti-inflammatory and immunological components in human milk.

In this population, the use of PDHM to achieve an all or near all human milk diet increases feeding tolerance and provides robust protection against serious complications while improving long term outcomes such as improved visual acuity and neurocognitive performance.[14]

One study found that premature infants who are fed an exclusive human milk diet are discharged, on average, 14 days sooner than infants receiving formula or a combination of maternal milk and formula.[15]

Necrotizing Enterocolitis

Most notably, an all or near all human milk diet dramatically reduces the risk of necrotizing enterocolitis (NEC), an inflammation of the intestine that is the most prevalent gastrointestinal emergency among

preterm infants. Up to 12% of infants born significantly premature develop NEC and will suffer both short-term and long-term health consequences. While all premature infants have an elevated risk for NEC, very low birth weight (VLBW) infants (those born at or below 1.5 kg), infants that have a history of ischemia (lack of oxygen) and babies with certain cardiac defects, are at particular risk.
Half of infants with NEC require surgery to remove the affected intestinal tissue. Of these, 25% will develop short bowel syndrome, a condition where there is not sufficient intestinal tissue for adequate absorption of nutrients. Short bowel syndrome is a devastating complication that requires years of therapy at best and multiple organ transplants at its worst.

NEC has a 24% overall mortality rate and a 40% mortality risk among infants who require surgery. NEC continues to require resources to alleviate long-term health problems associated with the disease, including intestinal obstructions, failure to thrive, feeding abnormalities, short bowel syndrome, parenteral nutrition-associated liver disease, and poor neurodevelopmental outcomes.

A review of 12 trials with a total of 1,879 infants showed significant increases in NEC risk in preterm infants who have received formula for supplementation.[16]

Human milk is uniquely designed for the newborn gut and provides robust protection. One study found that just 50% human milk feeding in the first 14 days of life was associated with a six-fold decrease in the odds of NEC.[17] This protection appears to be dose dependent with NEC rates lowering as the proportion of human milk in the diet increases.[18]

An exclusive human milk diet has been shown to decrease the overall incidence of NEC by up to 80% and the rate of surgical NEC by over 90%. Those infants who acquire NEC despite having an all human milk diet have a less serious course of disease, recover quicker and rarely require surgery.[19-23] A study of 227 "very premature infants" admitted to a single institution showed a dramatic drop in the incidence and severity of NEC after PDHM was introduced to the NICU.[24] In comparison to the 128 infants that received PDHM supplementation, the 99 infants that received formula had a higher incidence of NEC (9.1% vs 3.4%) and this increase was more pronounced in infants born between 28 and 32 weeks gestation (5.4% vs 0%). The unit also reported less frequency of surgical NEC following the introduction of PHDM.

It is estimated that one case of NEC could be prevented for every 10 infants receiving an all human milk diet, and 1 case of NEC requiring surgery or resulting in death could be prevented for every 8 infants receiving an all human milk diet.[25]

Total Parenteral Nutrition

Total parenteral nutrition (TPN) refers to intravenous feeding, bypassing the usual process of eating and digestion. TPN is often required in infants at 30 weeks gestation or below and infants with certain gastrointestinal conditions. TPN is a necessary but costly intervention and it is desirable to limit the time

on TPN as much as possible since prolonged use is associated with significant vascular, liver, and infectious complications.

Human milk, whether maternal or PDHM, is associated with quicker tolerance of oral feeds, eliminating the need to initiate TPN feeding in 11-14 % of premature infants or reducing the number of days on TPN.[26.27]

Gastrointestinal Anomalies

Infants with congenital or acquired gastrointestinal anomalies face surgeries, total parenteral nutrition (TPN), malabsorption issues, and multiple and/or extended hospital stays.

Defects in abdominal wall closure in which infants are born with the intestines, liver, or other organs outside of the body through the belly button (omphalocele) or a hole beside the belly button (gastroschisis) and other conditions such as atresia where portions of the intestine did not develop normally, require surgical intervention. An extended NICU stay is often necessary leading up to and after corrective procedures.

It is not surprising that human milk is better tolerated in infants with complex surgical GI anomalies. In a retrospective study of 140 infants with small bowel atresia or gastroschisis, those receiving PDHM to supplement mother's own milk had a shorter hospital stay (25 vs 35 days) and less central line (used for TPN) days (20 vs 28 days) in comparison to infants that were supplemented with formula.[28]

A similar positive benefit was found at the King's Daughters Children's Hospital in Virginia where 22 infants with gastroschisis who received a total human milk diet were found to achieve enteral feeds (nutrition delivered to the GU tract rather than TPN) sooner (median 5 days vs 7 days) and have a shorter time from the initiation of enteral feedings until hospital discharge (median 7 days vs 10 days) in comparison to 16 counterparts who received a full formula diet.[29]

Short bowel syndrome, a condition in which there is inadequate intestinal tissue for functional digestion is a common complication of NEC surgery but can also occur due to congenital anomalies. The condition can be life altering, causing significant disability, and requiring multiple therapies, surgeries and even transplantation. In 2008, a retrospective review of health care charges incurred by 41 children with short gut syndrome over a 10 year period showed the mean total cost of care per child for 5 years was $1,619,851.[30] These costs represent the significant burden of the morbidity endured by these children and their families.

Human milk feeding has been associated with improved outcomes and less time on TPN for infants with short gut syndrome and other gastrointestinal issues. In a study of 272 infants with intestinal failure followed for 27.5 months, human milk fed infants were on TPN for an average of 290 days vs. 720 days of TPN for infants not receiving human milk.[31]

Congenital Heart Disease

Infants born with congenital heart disease (CHD) are a diverse population with a number of challenges. Most notable are additional energy requirements and an increased risk for necrotizing enterocolitis.[32] These infants can benefit greatly from a human milk diet[33] but unfortunately, exclusive maternal breastfeeding success rates in this population may be decreased. These infants may be born at an appropriate weight and development for their gestational age, but many eventually develop growth and nutritional deficiencies which can exacerbate symptoms and negatively impact the postoperative course.

Infants with CHD are at an elevated risk for necrotizing enterocolitis independent of gestational age.[34] Those infants with both CHD and prematurity have been shown to have an even higher risk of NEC (13%) than preterm infants without CHD (9%).[35] While the risk of NEC decreases dramatically as gestational age approaches term for infants without CHD, even term infants with CHD are at increased risk. The risk differs by anomaly and for some lesions, especially those with cyanotic heart disease or single ventricle physiology, the risk can be as high as 11% to 20%.[36] NEC in term infants differs from preterm NEC, which has a much earlier onset[37] and higher mortality rates.[38] There is an abundance of evidence showing the protective effects of an all human milk diet for NEC in the preterm population. Given the elevated risks for NEC in the CHD population it is reasonable to include an all or near all human milk diet, using donor milk when necessary, in nutritional guidelines for cardiac newborns.[39]

Chylothorax

Chylothorax, an accumulation of chyle (fatty lymphatic fluid) in the pleural (membrane surrounding the lungs) space, is an occasional complication that develops in infants after cardiac surgery. This fluid can be very damaging to organs.

As the chylothorax resolves over the course of weeks, infants are managed on a low fat diet to reduce the formation of chyle. Maternal skimmed milk with the addition of MCT oil to replace fat is the preferred nutrition for infants with congenital or post-surgical chylothorax. There is evidence demonstrating that defatted PHDM results in satisfactory resolution of chylothorax when maternal milk is unavailable.[40]

Renal Disease

Infants with congenital or acquired kidney disease face a number of challenges and can benefit greatly from the immunological and nutritional support of PDHM.

For infants with impaired renal function, the renal solute load of any nutrition source is of major concern. Human milk is significantly lower in all substances related to renal solute load, except sodium (which is comparable) than specialized renal infant formula.[41,42] While protein levels are lower in human milk than specialized renal formula (1.35g versus 2.2g /100kcal)[43], improved nitrogen balance is seen in infants fed fortified human milk versus formula.[44] Improved nitrogen balance with human milk may

translate to a decreased need for additional protein fortification and accompanying increased renal solute load. PDHM retains the highly bioavailable protein content of human milk[45-47], and its comparable impact on nitrogen balance is noted in even early human milk research.[48,49]

Aluminum, a contaminant in specialized infant formulas (165mcg/L), is a serious concern with impaired renal excretion and is much lower in human milk (92mcg/L). During processing and distribution, PDHM is not exposed to the same aluminum contamination during bulk storage or dispensing containers, as donor milk is stored and dispensed in BPA-free plastic or glass.

Infants with Opioid or Substance Exposure

Neonatal Abstinence Syndrome (NAS), the withdrawal that occurs when an infant is born after exposure to drugs such as opioids in utero, is an increasing problem across the country and represents a significant health care cost burden. In a little over a decade, the incidence of NAS has tripled and the length of stay for NAS infants has increased, resulting in a seven-fold increase in NICU stays for drug exposed infants.[50]

Infants with exposure to opioids or other substances in utero may suffer from many side effects including tremors, increased muscle tone, high pitched crying, vomiting, rashes, poor feeding, poor weight gain, and diarrhea. If these symptoms are significant, neonatal pharmacotherapy is required to help the infant transition through withdrawal, leading to increased length of stay and additional healthcare costs.

Breastfeeding is associated with fewer symptoms of NAS and a decreased need for treatment.
At least seven observational studies have demonstrated that breast milk feeding decreases the risk for and severity of NAS.[51,52] In a Swiss study, only 26% of breast milk fed infants were treated for NAS compared with 78% of formula fed infants.[53] Similarly, breastfeeding was associated with a 79% decrease in the odds of an infant receiving treatment for NAS.[54] In Australia, among 190 mostly methadone-exposed infants, those fed breast milk were less likely to require pharmacologic treatment for NAS compared with those fed formula (53% vs. 79%, $p<.001$). They required lower doses of morphine, less often needed a second medication for NAS (7% vs. 17%), and had shorter treatment and hospital stay duration.[55]

A study in England of 444 methadone-exposed infants found a marked benefit of breast milk feeding for at least 72 hours on the treatment rate for NAS (OR 0.55).[56] One study demonstrated a dose effect for breastfeeding; predominantly breastfed infants had lower mean Finnegan scores than those partially breastfed, who had lower scores than those who were formula fed.[57] In a study of 60 infants, infants receiving an all maternal milk diet were shown to have decreased mean peak Finnegan scores (6.54 vs 11.54) and a shorter period of infant pharmacologic treatment (0.33 months vs 1.46 months) in comparison to infants receiving formula.[58]

It is widely believed that methadone or other treatment drugs such as Subutex in maternal milk is somewhat responsible for this effect, but research suggests that the amount of methadone in the milk of mothers under treatment is not significant enough to provide a therapeutic benefit to the infant.[59] While most studies show that the amount of methadone that passes into breast milk is small [60,61], there have been cases where abrupt weaning during higher dose maternal therapy has led to NAS in infants.[62]

Methadone and Subutex are safe during breastfeeding and mothers under treatment are encouraged to breastfeed. Despite this, and for a variety of reasons, most infants exposed to maternal opioids in utero do not have access to maternal milk.

Further research is needed to determine if decreases in NAS symptoms are due primarily to methadone or if breast milk itself eases symptoms and the need for treatment. GI issues and severe diaper rash are common problems in NAS so it may be that easily digested donor milk will provide benefit even in the absence of methadone. In a small pilot study, opioid exposed newborns showed a significant decrease in gastrointestinal symptoms using a donor human milk product instead of formula. These study results are severely limited due to the small sample size and the type of product used (unlike the pasteurized milk processed by non-profit milk banks, sterilized human milk products lack components that promote healthy microbiome development and important immune factors) but this data is encouraging and hints at the potential for the provision of donor milk to help this population.[63]

Increased Rate of Maternal Breastfeeding in the NICU

Nothing compares to mother's own milk as it is specifically designed for her infant's individual needs. Donor milk is meant to be a support to breastfeeding with the ultimate goal being the provision of mother's own milk.

In the NICU setting, the use of PDHM is associated with increased rates of exclusive maternal breastfeeding at discharge.[64] In an analysis of individual clinical data in the state of California from 2007-2013, the provision of donor milk was found to be associated with lower NEC rates and higher rates of maternal breast milk feeding at discharge.[65]

When a hospital starts a new donor milk program, the subsequent increase in maternal milk breastfeeding/pumping can be quite dramatic. Boston Medical Center looked at the use of mother's own milk (MOM) in VLBW infants for the two years prior to (N=74) and the two years after (N=80) the introduction of donor milk to the NICU. A 6-fold increase in the consumption of MOM and a 49% reduction in the cessation of MOM during the hospital stay was found after initiation of the donor milk program.[66]

Increasing Breastfeeding Rates and Reducing Risk in the Mother Baby Unit/Newborn Nursery

PHDM can play a vital role in the support of breastfeeding for well newborns in the Mother Baby Unit. A number of factors can delay the onset of copious milk production in the early days post-partum, including delivery by C-section, prolonged or traumatic labor and delivery, gestational diabetes, and

obesity. Due to this delay, newborns experiencing hypoglycemia (low blood glucose), hyperbilirubin (jaundice), or excessive weight loss may require supplementation in the first days of life. In addition to avoiding the risks of formula introduction and promoting the development of a healthy microbiome, the use of PHDM for medically necessary supplementation in well newborns may be associated with higher rates of exclusive maternal breastfeeding which ultimately optimizes long term outcomes for both mother and child.

The availability of PHDM may also decrease risks to the unit and individual newborns by reducing the incidence of families bringing milk that was pumped by someone other than the mother to the unit.

In a survey of 71 hospitals in Northeastern United States, 29% of the birth hospitals in Massachusetts and 43% of hospitals served by the non-profit milk bank in Massachusetts (representing several states) used PHDM in their well-baby population. Hospitals that used PDHM for healthy newborns had higher rates of maternal exclusive breastfeeding (77% versus 56%) and 83% of the responding hospitals viewed PHDM as an effective tool to increase their hospital's exclusive breastfeeding rates.[67] The effect of PDHM on breastfeeding success may extend well beyond the newborn period. A retrospective chart review of 122 infants that required supplementation at one Florida newborn nursery revealed that newborns that received PHDM were 5 times more likely to be exclusively breastfed at 6 months of life in comparison to their counterparts that received formula.[68]

Interviews of 30 postpartum breastfeeding mothers whose infants were given supplemental feeding of PDHM or formula revealed that PHDM is perceived as "healthier" and "temporary" whereas formula is seen as ongoing or permanent.[69]

Hypoglycemia is a common reason for supplementation in well babies in the first 24 hours of life. A study of new supplementing practices emphasizing the use of PDHM at one institution found a 10% reduction in NICU admission rates and a 22% increase in exclusive maternal breastfeeding rates. The median cost of PDHM was $13.73 per infant.[70]

Numerous studies have shown that human milk plays a significant role in the development of a healthy microbiome.[71-73] Emerging data suggest that ingestion of even small amounts of formula in the first few days postpartum may alter the normal colonization of the gut. In a study of 579 exclusively breastfed infants, the 179 infants that received small amounts of formula as newborns in the hospital had less richness and diversity of the microbiota and a lower abundance of bifidobacterial (beneficial bacteria) at 3 to 4 months of age in comparison to the infants that received no formula.[74]

Donor Milk Needs of Outpatients

PDHM may also be medically indicated for certain infants cared for at home with a variety of health conditions. Approximately 25% of the milk distributed by HMBANA accredited non-profit milk banks is used by outpatients.

Complex Medical Needs

Typical outpatient recipients are children with complex medical needs, often unable to thrive on other forms of nutrition. Common diagnoses include cardiac conditions, gastro-intestinal conditions, immune disorders, inborn errors of metabolism, formula intolerance, malabsorption disorders, post-surgical nutrition, renal disease, short gut syndrome, failure to thrive, and organ transplantation. Some of these outpatients require continuation of the PDHM use that began during the inpatient stay.

Newborns of HIV Positive Mothers

According to cdc.gov, less than 5,000 HIV positive women give birth in the US each year. With current medications and recommendations, perinatal transmission is rare with only 73 annual cases. HIV disproportionately affects communities of color in the US with Black populations accounting for over 40% of new HIV diagnoses and 64% of perinatal transmission cases.

It is known globally that HIV-exposed uninfected (HIV-EU) infants have increased morbidity and mortality.[75] Both in the United States and globally, hospitalization and infection related hospitalization rates for HIV-EU children aged 2 and under are higher in comparison to infants that were not exposed to HIV in utero[76] and the reasons for this are likely multifactorial. Changes in the microbiome of HIV-EU infants[77] may be one of the contributing factors.

Little data exists regarding donor milk use for HIV-EU infants and those studies that do exist have very small samples sizes of infants outside of the United States. Two such studies[78,79] suggest that HIV-EU infants that receive pasteurized donor milk have a larger thymus size in comparison to their formula fed counterparts and one found a lower incidence of infections.

Pasteurization of Mothers' Own Milk

Children with immunosuppressive disorders such as Severe Combined Immunodeficiency (SCID) or those undergoing bone marrow transplant (BMT) are at risk for serious infections. Emerging evidence suggests that human milk may have a beneficial effect on pro-inflammatory cytokines and the gut microbiome while reducing complications in children undergoing BMT. In a pilot study of children aged 6 to 40 months, graft versus host disease (17% vs.75%) and bacteremia (12.5% vs. 50%) were lower in the children receiving human milk (from mother or PDHM) in comparison to those receiving formulas in the period immediately following BMT.[80] Evaluation of the stool and blood of 38 children ages 0-5 in the early post BMT period showed decreased intestinal inflammation markers in the 23 children receiving human milk (from mother or PDHM) in comparison to controls.[81] The same team found differences in beta diversity in the human milk cohort compared to controls including decreases in Streptococcus spp. abundance at day 14 post BMT in those children that received human milk in comparison to those receiving formulas.[82]

Routinely, breastfeeding is restricted for mothers of infants with SCID and those undergoing BMT due to the risk of certain pathogens, such as cytomegalovirus (CMV), that can be passed through human

milk.[83,84] To allow infants facing such circumstances to continue to receive the protection and benefits of mother's own milk (MOM), some milk banks are able to pasteurize MOM in their milk labs. The use of MOM has many advantages as it is tailored to meet the age specific needs of the child and because the mother is interacting with the same environment, her milk is likely to include immunological factors specific to pathogens encountered by her child. It is also likely that the pasteurization of MOM will ultimately result in increased duration and success of breastfeeding as the mother will be actively pumping to supply milk during the at-risk period.

Cost Analysis

While the subset of infants that have a medical requirement for PDHM is quite small, they are a population with some of the most significant and complex medical issues, putting them at high risk for growth and neurodevelopmental challenges. These children may have considerable medical needs that extend well beyond infancy and many are high utilizers of healthcare resources throughout childhood.

The Burden of Prematurity

Significant prematurity and very low weight are two of the most expensive diagnoses in pediatric care. An Institute of Medicine (IOM) study, one of the largest reviews of its kind, identified preterm birth as a leading cause of neonatal morbidity, and disability resulting in an annual overall cost in the United States of at least $26 billion.[85] Medicaid finances approximately half of these healthcare costs.[86,87] Much of this burden is related to both acute and long-term complications, some of which may be prevented by or lessened through exclusive or near exclusive human milk feedings.

A retrospective cohort study analyzing the claims for the first six months of life of 763,566 infants commercially insured by Aetna between 2008 and 2016 illustrates the substantial costs associated with prematurity.[88] In comparison to a full-term birth which resulted in an average cost of $6370, infants born before 37 weeks gestation had claims averaging $76,153. Claims increased dramatically as birth weight and gestational age decreased with infants born below 2.5 kg (5.5lbs) incurring on average $114,437 of claims and infants born at 24 weeks gestation incurring $548,865 of claims. A cross-sectional study of 348,150 infants born at a Kaiser Permanente Northern California hospital between 2000 and 2011 yielded similar findings with costs increasing with decreasing gestational age.[89] In comparison to infants born at term, care costs for infants born at 32 weeks, 28 weeks, and 25 weeks gestation increase by 1339%, 3971%, and 5609%, respectively. Even slightly preterm births impacted cost of care with an increase of 178% at 35 weeks gestation.

PDHM's Role in Reducing the Healthcare Costs of Prematurity

The use of PDHM for supplementation to achieve an exclusive or near exclusive human milk diet reduces the incidence of some of the costliest complications associated with prematurity during the NICU stay and beyond. An analysis of extremely low birth weight babies (ELBW) born at 1000 g, found that failure to provide optimal human milk feeding was estimated to result in $21.1 million in direct medical costs, $563,655 of indirect medical costs, and $1.5 billion in costs due to premature death.[90] It has been

estimated that for every $1 spent on banked donor milk, $11 of health care costs due to length of stay, NEC, and sepsis reductions can be saved.[91] In an analysis of 207 VLBW infants, an exclusive human milk diet was shown to save 3.9 NICU days and $8,167.17 per infant.[23]

The Cost of Necrotizing Enterocolitis

A robust example of preventative medicine and cost containment in the preterm population is the use of PDHM to reduce the risk of NEC. It is estimated that NEC results in $5 billion of hospitalizations per year and approximately 19% of neonatal healthcare expenditures in the United States.[15] On average, a case of medical necrotizing enterocolitis results in $74,004 of additional care costs and one case of surgical necrotizing enterocolitis adds $198,040 or more.[23] The analysis of Aetna claims data previously mentioned showed NEC to increase the total cost of care by a multiplier of 1.91.[88]

In a retrospective analysis, one health system compared data from 150 VLBW infants who had their own mother's milk supplemented with formula prior to the implementation of the hospital's donor milk program and 169 VLBW infants who received PDHM for supplementation.[92] NEC rates were lower in infants receiving mother's own milk + donor milk in comparison to infants receiving mother's own milk + formula (1.8% vs 6.0%) and $1812 of costs were saved per percentage point decrease in NEC. The median costs of hospitalization plus feeding (2016 USD) were $15,555 lower for infants receiving mother's own milk + donor milk than infants receiving mother's own milk + formula.

The burden of NEC extends well beyond the initial hospitalization and newborn period. In a review of 50 surgical NEC survivors and 50 matched controls enrolled in the Texas Medicaid program born between 2002 and 2003, children with a history of NEC continued to have elevated health care costs at age 3. The mean incremental healthcare costs of the surgical NEC infants compared to controls between 6–12, 12–24 and 24–36 months of age were $ 18,274, $14,067 and $8,501 per infant per six month period, respectively.[93]

Surgery to treat NEC is the leading cause of pediatric short bowel syndrome, a condition where there is inadequate intestinal tissue leading to poor absorption of nutrients. Congenital intestinal anomalies such as gastroschisis are another major contributor. Short bowel syndrome is a devastating complication with high mortality rates that often requires years of therapies and interventions and can affect neurodevelopmental outcomes along with quality of life.[94] A retrospective review of the healthcare charges of 41 children with SBS over a ten year period illustrates the tremendous long term burden.[95] The mean total cost of care for the first year of life was $505,250 (2005 USD) ± $248,398, with inpatient hospitalizations accounting for most of these charges. In home health care costs increased each year reaching $184,520 at year five. The mean total care costs for the first five years of life was $1,619,851 per child.

Healthcare Costs and Savings Beyond NEC

While NEC prevention is often the primary driver of donor milk use in premature infants, a human milk diet provides powerful protection against other complications that are equally serious and costly

including bronchopulmonary dysplasia, sepsis, and retinopathy of prematurity. In the previously described analysis of data from a population of 763,566 commercially insured infants, these three conditions resulted in spending multipliers of 2.15, 1.29, and 1.16, respectively.

In a study of 291 VLBW infants, it was found that each ml of human milk fed per kg per day in the first 14 days of life saved $534 in non-NEC related NICU costs.[96]

Donor Milk Volumes and Feeding Costs in the Hospital Setting

Average PDHM volumes vary considerably according to individual hospital inclusion criteria, population served, and even the quality of lactation support. Of note, infants that are significantly premature often require the addition of fortifiers to either mother's own milk or donor milk to achieved recommended growth rates.

For 319 VLBW infants that required supplementation at one facility, the cost of feeding PDHM plus mothers' own milk was $1317 versus $936 for formula plus mothers' own milk.[92] An analysis of 281 infants supplemented with PDHM at Children's Hospital of Philadelphia yielded a mean length of use of 23 days and a mean daily volume of 195ml resulting in an average cost of $29.19 per infant per day for a total cost of $671.37 based on a milk processing fee of $4.50 per ounce.[97]

[Of 64 VLBW infants born < 33 weeks gestation at one level III NICU, 72% received supplemental feedings of PDHM.[1] Costs per infant ranged from $27- $590 USD 2003 with a mean of $236.90. Only 15% of these infants required exclusive feedings of PDHM. Costs were based on a price of $4.00/oz while the current average milk processing fee in the United States is $4.50/oz.]

A Note About Mother's Own Milk

Mother's own milk provides unparalleled benefits in terms of nutrition, immunological support, and protection from complications. While PDHM can be lifesaving, it is altered due to the mismatch in the age of the donors' babies and the necessary heat processing to inactivate pathogens and, therefore, cannot compare to mothers' own milk. An overlooked cost benefit of donor milk is its association with increased exclusive maternal breastfeeding success and overall increased volume of mother's own milk consumed as described earlier. The most effective way to reduce complications and improve long term outcomes with human milk is through comprehensive lactation support and educational programming of which PDHM is only one aspect.

Economic and Racial Disparities in the Hospital Setting

The use of PDHM has become the standard of care for at risk neonates in most parts of the United States but significant disparities exist.

The number of hospitals which have PDHM available in their advanced care units has steadily increased over the past two decades with most level III and IV NICUs at least utilizing PHDM for extremely low

birth weight infants. Data collected in the Centers for Disease and Prevention National Maternity Practices in Infant Nutrition and Care Survey showed the percentage of level II and III NICUs using PDHM in the United States increased from 21.2% in 2007 to 30.8% in 2011.[98]

PDHM usage and criteria were found to vary widely in a survey of 153 medical directors of level III and IV NICUs of which 59% of respondents reported have PHDM available in their unit.[99] The availability of PDHM was more common in hospitals that participate in the Vermont-Oxford Network (OR 4.6) and those that care for more than 100 VLBW infants per year (OR 2.2). Criteria varied by birth weight (<1.0g to <1.8g) and gestational age (<28 weeks to <34 weeks). Of note, the risk for NEC is still greatly elevated for infants up to 34 weeks gestation and even longer for some.[88,89]

The most recently published estimate of donor milk use in the United states reported findings from a 2017 survey of 120 randomly selected hospitals, 88% of level III and IV NICUs reported having donor milk programs.[100] Unfortunately, safety net hospitals (> 75% of patients are Medicaid recipients) were much less likely to use PDHM (aOR 0.3).

Prematurity disproportionately impacts non-white populations. Black mothers have a higher risk of delivering prematurely, their preterm births are earlier, and they are more likely to have recurrent preterm birth.[101] In comparison to non-Hispanic white infants, Hispanic and non-Hispanic black infants have increased rates of NEC, bronchopulmonary dysplasia, retinopathy of prematurity, intraventricular hemorrhage, and even mortality.[102,103] Hispanic and non-Hispanic black infants that develop NEC are more likely to die than non-Hispanic white infants that suffer from NEC.[104]

Unfortunately, fewer black infants have access to both mother's own milk (CDC, 2018), and PHDM, further increasing these infants' risk of complications and death. A study of NEC incidence and human milk use among 47,112 VLBW infants born in California between 2008 and 2017 revealed significant racial differences. While the trend was that infants of all races enjoyed increasing amounts of human milk at NICU discharge, non-Hispanic black infants consistently received the lowest amounts. Human milk use at discharge was shown to account for 22% of the total risk of NEC in non-white vs. white infants, and 44% in black vs. white infants.[105] The use of both mother's own milk and PHDM was even found to be lower in NICUs located in postal codes with higher percentages of black residents in an analysis of data from the CDC's 2015 Maternity Practices in Infant Nutrition and Care survey.[106]

Significant sociodemographic differences in the use of PDHM in the well-baby unit were revealed in a retrospective study of 584 mother baby dyads admitted to a postpartum unit between 2017 and 2019.[107] Infants born to white, non-Hispanic mothers were more likely to receive PDHM than formula for medically indicated supplementation than those born to mothers who are black (aOR 2.7), Hispanic (aOR 3.0), or Asian American (aOR2.7)

Outpatients

Outpatients with certain medical issues derive tremendous benefit from PHDM but face significant access issues. They children are a diverse group with various conditions. Severe formula intolerance and allergies where infants are not thriving even with specialty formulas are common indications for PDHM. Some outpatients received donor milk as inpatients and must continue after discharge. The vast majority of inpatient PHDM recipients are exclusively fed by their mother's own milk or have transitioned to commercially available formulas prior to discharge but on rare occasions, infants are unable to transition to formula, even after several trials. Most often, outpatient recipients have unique and complex sets of circumstances that require PHDM, making it difficult to quantify a cost benefit analysis. For these children, who are outliers in terms of healthcare utilization, it is likely that PDHM is decreasing readmissions and preventing more invasive and costly interventions while optimizing growth to maximize neurodevelopmental outcomes.

High Cost and Risky Alternatives

The donor screening, milk testing, and processing that is required to make PDHM safe results in costs that are higher than commercial formulas. Due to the large volumes consumed by infants who weigh enough to be cared for at home, PDHM is unaffordable for all but a few families. Coverage for PDHM is critical in making PHDM feasible for the outpatient population. In the absence of coverage, some parents resort to making pleas for milk on social media or even purchasing milk online. Such practices can be risky for any baby but particularly for babies that are already compromised due to medical issues.

Some non-profit milk banks offer income based sliding scale programs or even free care for families when PDHM is not covered but these supports do not adequately meet the need. The PDHM processing fees charged by non-profit milk banks generally represent the true cost of milk processing, leaving limited resources for charitable care.

Inconsistent Coverage and Availability

An internal survey of HMBANA accredited non-profit milk banks revealed inconsistencies in insurance coverage across the United States with many areas having little to no insurance support for outpatient PDHM. As a result, the majority of milk banks are unable to support having an outpatient program that adequately meets the needs of their service area.

Pennsylvania Data

Births

According to pa.gov, 134,247 live births occurred in the Commonwealth in 2019. Of the infants born that year, 11,311 were low birth weight (under 2.5kg) and 1931 of them were very low birth weight (under 1.5kg) putting them at extremely high risk for NEC and other serious complications.

Necrotizing Enterocolitis (NEC) Occurrence and Cost

The following data was compiled by the Pennsylvania Health Care Cost Containment Council and demonstrates the devastating impact of NEC on the children of the Commonwealth.

2018 and 2019 Newborn Hospitalizations

	2018		2019	
	Number	Percent	Number	Percent
Number of hospitalizations for patients 0-28 days old	132,144	100.0%	129,963	100.0%
with				
Birth Weight < 1,000 grams	866	0.7%	829	0.6%
< 24 weeks of Gestation	252	0.2%	226	0.2%
Necrotizing Enterocolitis	253	0.2%	206	0.2%

Length of Stay

	2018		2019	
	Average	Total	Average	Total
Length of stay in days:				
All 0-28 days old	4.0	528,415	4.0	518,198
0-28 days old with NEC	61.4	15,524	60.6	12,492

NEC Related Hospitalization Charges

	2018		2019	
	Average	Total	Average	Total
Hospital charges:				
All 0-28 days old	$26,897	$3,554,340,168	$28,252	$3,671,759,638
0-28 days old with NEC	$831,532	$210,377,708	$850,462	$175,195,201
NEC in medical DRGs	$703,133	$161,720,546	$699,462	$136,395,122
NEC in surgical DRGs	$2,115,529	$48,657,162	$3,665,425	$36,654,251

NEC protection can be optimized through consistent, evidence based use of donor milk across Pennsylvania. Based on 2019 figures, if just one infant with NEC is able to avoid surgery, the savings would exceed the total estimated costs of donor milk across Pennsylvania. Of note, these costs only represent the newborn stay and do not provide insight into the additional long-term costs and impact of NEC across childhood.

Donor Milk Use

Donor milk use has been the standard of care in many parts of the US for several decades but has only recently become commonplace in Pennsylvania. In 2015, prior to the opening of Mid-Atlantic Mothers' Milk Bank in Pittsburgh, approximately 35% of the level III and IV NICUs in Pennsylvania used PDHM with no NICUs in southwestern Pennsylvania utilizing it. In 2018, Pennsylvania reached an important milestone with 100% of level III and IV NICUs having PDHM available for at risk premature babies.

Hospital donor milk practices across the Commonwealth have continued to evolve but inclusion criteria are very inconsistent with many infants who are at increased risk for serious complications such as NEC or sepsis not being offered PDHM. Safety net hospitals and others with limited resources continue to have very strict eligibility criteria, reserving PDHM only for only the tiniest infants at or below 1250g or 1500g (2.75 lbs. or 3.3 lbs. Some systems with greater resources have been able to expand criteria to include other infants with elevated risk such as those with gastro-intestinal and cardiac conditions along with increasing weight requirements to 1800g (or more) and below. Only a tiny minority of hospitals in Pennsylvania are offering donor milk in their Mother Baby Unit for near term or full term infants that medically require supplementation.

As previously mentioned, outpatients who have a medical need for donor milk suffer from complex and serious medical issues. Their access to donor milk is usually dictated by insurance coverage. The majority of outpatients with medical requirements served by Mid-Atlantic Mothers' Milk Bank are Medicaid recipients who are members of MA Managed Care Organizations (MCOs). A handful of MCOs and commercial health plans have written donor milk policies and the coverage criteria vary considerably among them. The non-profit Mid-Atlantic Mothers' Milk Bank is the primary supplier of outpatient PDHM to outpatients in Pennsylvania and since opening its doors, has worked to educate and develop relationships with regional plans. As a result, coverage has much improved but is inconsistent, leaving many children with severe medical needs unable to receive the donor milk that they need to thrive.

Discussion

The use of pasteurized donor human milk (PDHM) is now the accepted standard of care for premature and medically fragile infants in most parts of the United States. Robust evidence spanning decades clearly demonstrates that PDHM in the absence of maternal milk provides powerful protection from many complications including NEC, a major cause of mortality, morbidity, and disability in the NICU setting. Children that suffer from NEC or other significant NICU complications face serious medical and neurodevelopmental issues in the newborn period and often for years thereafter, resulting in this population being some of the highest utilizers of healthcare resources in all of pediatrics.

Significant racial and economic disparities surround human milk availability. Nationally, PDHM donor milk is less likely to be utilized in settings that care predominantly for Medicaid recipients and non-white infants being cared for in the NICU have less access to human milk, both maternal and PDHM. These are

populations that have higher rates of prematurity, mortality, and morbidity along with poorer outcomes when they encounter NICU complications.

As evidence mounts and donor milk use evolves to include more diagnoses and populations, some at-risk infants are being left behind in Pennsylvania. While all of the highest level NICUs in the Commonwealth now utilize donor milk, the criteria for its use varies considerably, with higher resource institutions having the broadest criteria. Asa result, many hospitals are not using PDHM for all babies that are at increased risk for NEC and serious complications. Typically, PDHM is covered as part of the DRG, or case rate, in Pennsylvania. Carving PDHM costs that meet evidence-based criteria out of the DRG has the potential to provide the consistency that will optimize the prevention of NEC and other complications thereby reducing the costs associated with an acute hospital stay and long term sequela.

Until recently, discussions of the use of PHDM have largely been confined to the NICU population. Emerging evidence suggests that other populations, both inpatient and outpatient, derive significant benefit from the provision of PDHM. Over the past decade, the number of milk banks in the United States has grown considerably, reaching a level that can provide a reliable, ample supply to meet any medical need here in Pennsylvania, primarily through the Mid-Atlantic Mothers' Milk Bank, and across the country.

Outpatients that medically require donor milk are difficult to describe since they are a small but diverse group, often with complex medical issues. Cost is the main access barrier to medically required outpatient PDHM both individually and regionally. Insurance coverage for outpatient PDHM is inconsistent but is crucial given the costs of screening, testing, and processing donor milk. In the absence of coverage, families must rely on the charitable care programs provided by non-profit milk banks which are neither adequate nor sustainable. Even infants that are doing poorly on elemental specialty formulas, meaning that they have exhausted oral nutrition options, sometimes have difficulty accessing donor milk, putting them at serious risk for growth and development issues. Evidence-based PDHM coverage for outpatients could improve the outlook for some of the smallest and most fragile residents of Pennsylvania.

In summary, PDHM is an underutilized resource and its use can be optimized to improve outcomes and reduce care costs for selected infant populations. While many hospitals and some health plans have stepped up to meet these needs, substantial gaps remain.

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