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Oropharyngeal Therapy with Mother's Own Milk (OPT-MOM) to Protect Extremely Premature Infants against Infectious Morbidities

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Abstract

Background: Upon birth, the extremely low birth weight (ELBW) infant experiences an abrupt cessation of amniotic fluid exposure. The ELBW infant's oropharynx is no longer exposed to immunoprotective biofactors, which modulate the immune system and promote maturation of the gastrointestinal tract. Many immune and trophic biofactors are also contained in the mother's own milk, and are especially concentrated in the milk expressed by mothers of ELBW infants; particularly in colostrum. Unfortunately, clinical instability precludes enteral feeding for ELBW infants in the first days of life. Once started, enteral feeds are administered via a nasogastric tube; therefore oropharyngeal exposure to protective milk biofactors cannot occur until the infant begins per oral feeds, with mother's milk; typically at 32 weeks corrected gestational age. The delay, or lack of, oropharyngeal exposure to protective milk biofactors, during the critical first weeks of life for the ELBW infant, may be contributing substantially to prematurity-associated infectious morbidities. Oro-Pharyngeal Therapy with Mother's Own Milk (OPT-MOM)-placing drops of mother's milk onto the infant's oral mucosa to provide early postnatal modulation of the immune system- can serve as a potential substitute for amniotic-fluid (biofactor) exposure. Purpose: To describe how OPT-MOM may protect the ELBW infant against prematurity-associated infectious morbidities including Late-Onset Sepsis, necrotizing enterocolitis (NEC), and also Ventilator-Associated Pneumonia. This manuscript will provide neonatal clinicians with the latest evidence to guide clinical practice. Important implications, in terms of patient safety, will also be addressed.

Keywords: breastmilk, human milk, mother's milk, colostrum, oropharyngeal, oral immune, oral care, premature, extremely low birth weight, very low birth weight.

Introduction

Extremely low birth weight (ELBW) infants are born at the lower limits of viability, weighing less than 1000 grams, and experience an abrupt ending to amniotic fluid exposure. The oropharynx is no longer bathed with amniotic fluid biofactors which provide immunostimulatory effects, protect against infection, and promote gastrointestinal maturation. Protective biofactors are also contained in mother's own milk, with the highest concentrations present in the milk expressed by mothers of ELBW infants; especially in colostrum. However, with our current standard of care, the ELBW infant's oropharynx is not exposed to protective milk biofactors, for up to 10 weeks post-birth. Enteral feedings are administered via a nasogastric tube; which bypasses the oropharynx, until per oral feedings are introduced at >32 weeks corrected gestational age (CGA). It is possible that the lack of oropharyngeal exposure to protective biofactors, for a prolonged period post-birth, may be contributing to prematurity-associated infectious morbidities for the ELBW infant, including Late-Onset Sepsis (L-OS), Necrotizing Enterocolitis (NEC), and Ventilator-Associated Pneumonia (VAP). This deficit has never been addressed in neonatal care. Oro-Pharyngeal Therapy with Mother's Own Milk (OPT-MOM)-placing drops of mother's milk onto the infant's oral mucosa- may serve as a natural substitute for amniotic fluid exposure; potentially correcting this deficit. This paper will present evidence that supports the concept that OPT-MOM may serve as a potential immunotherapy, to protect ELBW infants against infectious morbidities.

Prematurity-associated Infectious Morbidities

ELBW infants are at high risk for acquiring L-OS, NEC, and VAP; infections which are associated with significant mortality, costly morbidities, and the potential for adverse long-term neurodevelopmental outcomes. Late-onset sepsis (L-OS) is defined as the identification of pathogenic organisms from a blood culture (bacteremia) acquired after the third day of life. (1) LOS affects 32-53% of ELBW infants, with high mortality (30%) (2,3) and increases hospitalization costs by 31%. (4) Necrotizing Enterocolitis (NEC) is a gastrointestinal infectious and inflammatory disorder, which in severe cases can lead to bowel necrosis and death. (5-12) NEC affects 10-15% of ELBW infants, with 30% mortality and costs an estimated $1 billion in healthcare dollars yearly. (8-10) Ventilator-associated pneumonia (VAP) accounts for up to 32.3% of NICU device-associated infections, is associated with secondary bacteremia and chronic lung disease, and prolongs hospitalization. (13,14) With the increased survival of ELBW infants, the incidence of prematurity-associated morbidities, and their associated costs, are on the rise. (15) The prevention of infectious morbidities, including L-OS, NEC, and VAP, is a clinical priority.

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Infection Risk for ELBW Infants

ELBW infants are at high risk for acquiring L-OS, NEC, and VAP as a result of numerous factors. First, they have an abnormal host defense, with deficits in both innate and adaptive components of the immune system. The immature immune system is unable to mount an effective, appropriate response against pathogens encountered; often resulting in unbridled inflammation with subsequent tissue injury. (16-19)

Second, ELBW infants require multiple invasive catheters and

tubes for the provision of life-saving therapies. These devices become portals for pathogen entry. Bacterial colonization of the oropharynx and upper respiratory tract increases the risk for VAP, while bacterial colonization of the gastrointestinal tract increases the risk for both L-OS and NEC. Third, ELBW infants have an immature gastrointestinal tract which increases infection risk. Clinical instability in the first days of life often precludes enteral feeds for ELBW infants. The lack of enteral nutrition during this critical post-birth period quickly leads to intestinal atrophy, (20) which places the infant at risk for feeding intolerance and also NEC. Once feeds are initiated, the immature gastrointestinal tract makes the tolerance of enteral feeds problematic, and leads to a prolonged time to reach full enteral feeds. This necessitates the provision of prolonged parenteral nutrition, via centrally-placed venous catheters, factors which increase the risk for L-OS. Also, a prolonged time to reach full enteral feeds is linked to a higher risk for NEC. (12) Fourth, ELBW infants require a prolonged hospitalization; typically 3-4 months and therefore have persistent exposure to neonatal intensive care unit (NICU) pathogens. Finally, ELBW infants develop an abnormal gastrointestinal microbiome (dysbiosis) as a result of exposure to antibiotics, delayed enteral nutrition, and immaturity in gastrointestinal function including decreased peristalsis, decreased gastric acid and enzymatic activity, reduced surface glycoconjugates, and decreased intestinal mucus. (1,21,22) Gastro-intestinal pathogens can injure the fragile immature intestinal mucosal barrier; an initial step in NEC pathogenesis. Also, decreased tight junctions between intestinal epithelial cells facilitate bacteria translocation, with subsequent L-OS.

A pathogen-predominant microbiome is an important component in the pathogenesis of both L-OS and NEC. (1,5,19,21-25) Interventions that optimize the microbiome and reduce the presence of pathogens, in the gastrointestinal tract and the oropharynx, may reduce the risk for L-OS, NEC, and VAP for the ELBW infant.

Protection against Infection with Mother's Own Milk (MOM)

Mother's milk feedings have been linked to improved health outcomes for premature infants, including protection against several prematurity-associated morbidities including NEC, L-OS, retinopathy of prematurity, chronic lung disease and adverse neurodevelopmental outcomes. (2,4,12,15,26-38) These health benefits are attributed to a multitude of potent biofactors which collectively: provide antimicrobial activity, maintain intestinal integrity, provide anti-oxidant, anti-inflammatory and immunomodulatory functions, and provide trophic/maturational effects on the intestinal mucosa. (39-44) Biofactor concentrations are highest in the milk expressed by women who deliver the least mature (ELBW) infants; (45-54) particularly in early milk (colostrum). However, even beyond the colostral phase, concentrations of several immune and trophic biofactors remain high in preterm milk (compared to term milk) for many weeks post-delivery. 50, 53, 55 Importantly, many of these protective biofactors are also present in amniotic fluid. These gestation-specific trends in biofactor concentrations suggest that preterm milk has an important biological function for facilitating extra-uterine transition for the ELBW infant. Preterm milk is therefore uniquely suited to compensate for the ELBW infant's immunological deficiencies; providing protection against infection.

"By adding these exceptional presenters to the long list of local experts who typically present at the Stanford NeuroNICU course this two-day seminar offers the best way for anyone interested in the neonatal brain to become immersed in the best science and practical bedside approaches for caring for a variety of infants with, or at-risk for, brain injury."

A Universal Clinical Dilemma:

Early post-birth exposure to mother's milk may serve as a potential immune therapy for the ELBW infant. Unfortunately, enteral exposure post-birth is often delayed for several days due to clinical instability. Once the infant is stable, minimal enteral feeds are initiated via a nasogastric tube, which bypasses the infant's oropharynx. Oral feeds (breast and/or bottle) are typically not introduced until the ELBW infant reaches a corrected gestational age (CGA) of at least 32 weeks. Therefore, with our current standard of care, oropharyngeal exposure to protective (milk) biofactors is delayed for up to 10 weeks post-birth, for the least mature ELBW infants born as early as 22 weeks gestation. Unfortunately, many mothers of ELBW infants become discouraged with low milk volume and discontinue milk expression before the infant is ready to begin oral feeds. In these cases, when own mother's milk is no longer available, and standard formula is given instead, the ELBW infant's oropharynx is never exposed to

protective biofactors post-birth. This deficit- the delay or complete lack of biofactor exposure post-birth for the ELBW infant- has never been addressed in neonatal care. In a healthy term pregnancy, the fetus receives continuous in-utero exposure to (amniotic-fluid) biofactors until 40 completed weeks of gestation. It is plausible that the delay (or lack) of oropharyngeal exposure to (immune and trophic) biofactors post-birth may be contributing significantly to the pathogenesis of prematurity-associated infectious morbidities. Oropharyngeal administration of mother's own milk, using the OPT-MOM approach, may serve as a potential natural alternative to provide a continuum of amniotic fluid effects ex-utero for the ELBW infant.

OroPharyngeal Therapy with Mother's Own Milk (OPT-MOM)

The OPT-MOM approach involves a rigorous protocol of frequent and precise dosing of mother's own milk, administered via the oropharyngeal route, for several weeks until per oral feeds can be safely introduced for the ELBW infant. The goal is to provide sustained oropharyngeal exposure to protective (immune and trophic) milk biofactors, similar to those that are naturally found in amniotic fluid. Treatments are started soon after birth, once mother's colostrum is available, and continued for many weeks without interruption.

Since OPT-MOM is intended to serve as an ex-utero substitute for biofactor-rich amniotic fluid exposure, the protocol includes the use of colostrum, transitional and mature milk for sustained dosing over several weeks post-birth; until the infant reaches 32 weeks CGA. The dosing is precise (0.2 mL; ~ 8 drops) in order to expose the infant to biofactor doses comparable to in-utero exposure. For example, based on concentrations of epidermal growth factor (EGF) and lactoferrin in human amniotic fluid and preterm milk, (45,55) a fetus weighing 1000 grams would be exposed to 38 ng of EGF and 172 mcg of lactoferrin daily via amniotic fluid (200 mL/kg fetal weight/day). Ex-utero, an ELBW infant weighing 1000 grams, would receive a 'dose' of 396 ng of EGF and 658 mcg of lactoferrin with OPT-MOM treatments every 2 hours (2.4 mL/daily), and 216 ng of EGF and 450 mcg of lactoferrin with treatments every 3 hours (1.6 mL day). Thus, OPT-MOM can potentially provide higher doses of protective biofactors for the ELBW infant, who remains in the pathogen-laden NICU, compared to the sterile in-utero environment for the fetus. The amount of milk that is needed daily for OPT-MOM treatments is minimal; less than a teaspoon (1.6 – 2.4 mL, depending on the frequency of treatments), therefore even mothers with minimal milk volume can easily provide this volume daily.

OPT-MOM: Potential Mechanisms of Action

FIGURE 1

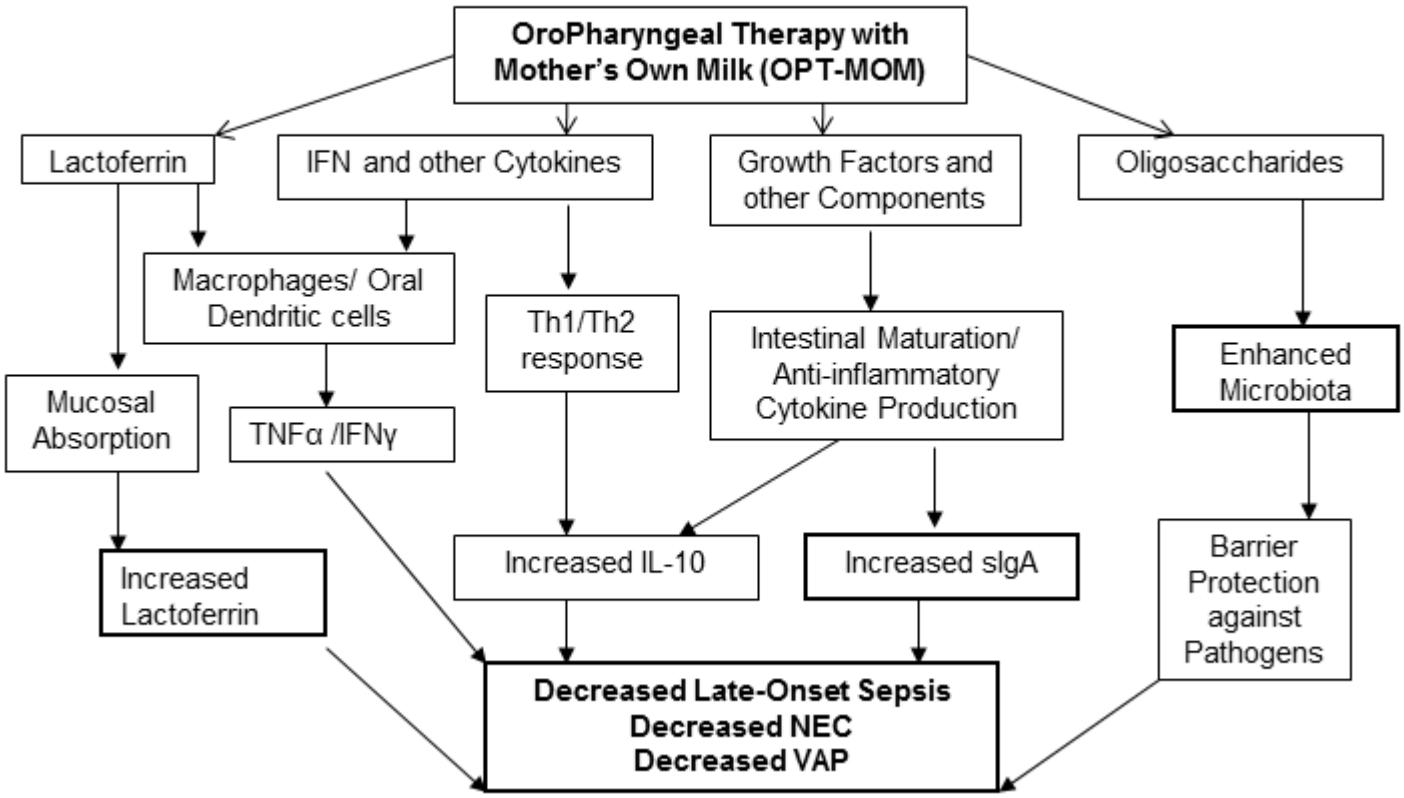

Figure 1: OroPharyngeal Therapy with Mother's Own Milk (OPT-MOM).
A simplified model of the proposed mechanisms of action for protection against Late-onset sepsis, NEC and VAP, using the OPT-MOM approach, based on the known biological functions of milk biofactors.

The potential benefits of OPT-MOM are based on the following distinct mechanisms: (1) immunostimulatory effects of cytokine interaction with immune cells within the oropharyngeal-associated lymphoid tissues (OFALT), (2) passive mucosal absorption of protective (immune and trophic) biofactors, (3) barrier protection against pathogens in the oropharynx, (4) anti-inflammatory protection, (5) local and systemic effects of oligosaccharides, and (6) protective effects of antioxidants. These mechanisms are detailed elsewhere, (60, 61) but summarized below and in Figure 1.

Biofactors provide protection against L-OS with antimicrobial, anti-inflammatory and immunomodulatory functions and the creation of a gastrointestinal microflora milieu that prevents the proliferation, and translocation of pathogenic organisms. (61) Trophic factors promote intestinal maturation, which facilitates the tolerance of enteral feeds and thereby indirectly protect against L-OS, since central venous catheters can be removed earlier.

Protection against NEC is attributed to biofactors which promote the presence of commensal bacteria; reducing dysbiosis. Also, other biofactors provide antimicrobial properties, maintain the integrity of the intestinal epithelial barrier, heal areas of intestinal

Table 1. Oropharyngeal Administration of Mother's Milk

• Oral care/mouth care with colostrum
• Oral swabbing with colostrum
• Buccal swabbing with colostrum
• Oral colostrum
• Oropharyngeal colostrum (OC)
• Mouth feeds with colostrum
• Oral immune therapy (OIT) with colostrum
• Colostrum oral care (COC)
• Oral human milk swabbing
• Buccal administration of colostrum
• Oral colostrum priming (OCP)
• Colostrum swabbing
• Oropharyngeal Therapy with Mother's Own Milk (OPT-MOM)
• Administración de calostro orofaríngeo

injury, decrease inflammation, provide anti-oxidant protection, promote intestinal maturation and regulate the ELBW infant's immune response. (60)

Protection against VAP is afforded by human milk oligosaccharides, secretory immunoglobulin A (sIgA) and lactoferrin, among others. Oligosaccharides and secretory IgA provide barrier protection and inhibit the adhesion of respiratory pathogens to epithelial cell surface receptors in the mucosa of the oropharynx. This may lessen the ability of the pathogens to colonize the upper respiratory tract where they could lead to subsequent VAP. Lactoferrin and oligosaccharides also provide antimicrobial, anti-inflammatory and mucosal healing properties (60,61) which serve to protect against VAP.

With OPT-MOM, the interaction of (milk) cytokines with immune cells within lymphoid tissues may provide systemic immunostimulatory effects and anti-inflammatory protection. Mucosal absorption of immune biofactors, such as lactoferrin, may provide systemic protection against infection, while absorption of trophic factors (e.g., EGF), may accelerate intestinal maturation. Oligosaccharides may also be absorbed mucosally with systemic effects or may travel to the gut; enhancing the microbiota and decreasing the risk for intestinal injury. (60,61) Oligosaccharides, sIgA, and lactoferrin, prevent pathogen attachment to the oropharyngeal and intestinal mucosa, providing protection against VAP, L-OS, and NEC. Figure 1 depicts the proposed mechanisms of action for protection against L-OS, NEC, and VAP, using the OPT-MOM approach, based on the known biological functions of milk biofactors.

Current Evidence to Support the OPT-MOM Approach

The concept of using oropharyngeal administration of mother's colostrum as a potential immune therapy for ELBW infants was first introduced into the medical literature in 2009. (62) Following the publication of this initial "theory paper," two pilot studies 56, 63 established feasibility, and results from a small randomized controlled trial (RCT) (57) were suggestive of possible immunostimulatory effects. Infants who received oropharyngeal (own mother's) colostrum, were found to have higher concentrations of urinary lactoferrin, compared to placebo-treated infants. A clinically relevant large effect size (1.30) was noted for urinary lactoferrin in treated infants, suggesting that results may have reached statistical significance with a larger sample. The most compelling finding was that treated infants reached full enteral feedings (150 mL/kg/day) on average ten days earlier (14.3 ± 5.7 vs 24.2 ± 8.7; p=0.032) compared to controls. (57) The intervention was feasible and well-tolerated by all enrolled infants. Infants were noted to begin sucking on the breathing tube when the drops were being administered.

Since these initial studies were first published, several researchers have evaluated the benefits of oropharyngeal mother's milk for premature infants; particularly with the very low birth weight (VLBW; BW<1500g) and ELBW population. Although variable terminology has been used to describe 'oropharyngeal administration of mother's milk' (see Table 1) including 'oral immune therapy' the concept is the same; placing drops of mother's milk onto the infant's oral mucosa in efforts to provide early postnatal modulation of the immune system. To date, the oropharyngeal administration of mother's milk has been associated with many benefits for the recipient preterm infant, including: enhanced immune status (higher concentrations of serum IgA, (66) salivary sIgA, (64) urinary sIgA, (65), salivary lactoferrin, (69) and urinary lactoferrin,67), reduced inflammation (lower concentrations of salivary IL-8 and TGFβ-1 and also urinary IL-1β,) (65) a lower risk for clinical sepsis, (65,67) enhanced oral microbiota, (68,69) enhanced breastfeeding outcomes, (58) improved growth, 70 a reduced time to achieve full enteral feedings (67,69,70) and full per oral feedings, (69) and a reduced length of hospital stay. (69)

More recent work suggests that this intervention may also be beneficial for term infants who are unable to feed orally; including infants with cardiac disease, congenital diaphragmatic hernia, omphalocele, gastrointestinal anomalies (including gastroschisis) and also infants who are recovering from surgery. (71-74) Potential maternal benefits have also been reported. (58,74,75) Evidence suggests that mothers who provide milk for oropharyngeal administration, may be more motivated to continue milk expression ('pumping'); thus maintaining lactation during their infant's hospitalization, even while the infant is not able to feed enterally. (75) Also, the provision of oropharyngeal colostrum has been linked to sustained mother's milk feedings, for VLBW infants at six weeks of age and through discharge from the neonatal intensive care unit. 58 This suggests that providing milk for oropharyngeal administration to their preterm infant may be a strong motivating factor for mothers to continue pumping, resulting in more 'doses' of milk for the preterm infant, during the first weeks of life.

Discussion and Clinical Implications

In published reports, the oropharyngeal administration of mother's milk is described using variable terminology (see Table 1) yet the underlying premise is the same: placing drops of mother's milk onto the infant's oral mucosa so that (milk) biofactors may provide immunomodulation. While prior studies focused on the use of early milk (colostrum) for a brief 48-hour treatment period for infants who were 'nil per os', a paradigm shift has occurred and clinicians are now utilizing oropharyngeal administration of mother' own milk (inclusive of early, transitional and mature milk) for longer treatment periods; up to day of life 7. Yet, it is unlikely that brief treatment periods (2-7 days) will have a significant impact on important clinical outcomes such as NEC. The latest terminology (OPT-MOM) implies the prioritized use of oropharyngeal mother's milk, as a potent immunomodulatory therapy over several weeks post-birth. In this manner, OPT-MOM serves as an adjunct to nasogastric-tube-feedings and as a natural substitute for amniotic fluid (oropharyngeal) exposure until per oral feeds (via breast and/or bottle) can be safely introduced for the ELBW infant. A multi-center RCT is underway (funded by the Gerber Foundation), utilizing the OPT-MOM approach and evaluating its impact on clinical outcomes for recipient ELBW infants. (61)

Current evidence suggests that oropharyngeal administration of mother's own milk can be beneficial and without adverse effects for recipient infants. However, safety and efficacy have not been firmly established in an adequately-powered RCT. To date, published studies are primarily retrospective in design, utilized very small samples, and were not powered to look at clinical outcomes. Also, the treatment periods were brief, ranging from 48

hours to 7 days post-birth. An important consideration is that the immune benefits did not always persist once the treatments were stopped.

In a recent study, even with a treatment period of 5 days of oropharyngeal milk administration, the immune effects that were noted at one week of life for treated infants, were not sustained when measured at two weeks of life. (64) The authors speculate that the lack of effect on clinical outcomes may have been due to the short 5-day duration of the treatment protocol and that the immune benefits (higher concentrations of salivary sIgA) may have been sustained with longer duration of the treatment protocol. 64 In another recently published study, 68 the investigators suggest that a brief 48-hour treatment period may have limited effects on oral microbiota or clinical outcomes such as NEC, L-OS VAP, and chronic lung disease. In a third recent study, the authors suggest that more research is needed to determine if the immune effects are passive and therefore treatments should be continued and if the intervention results in temporary or sustained changes. 69 In a fourth and most recent study; a placebo-controlled RCT (n=64 VLBW infants), salivary IgA was significantly increased from baseline levels in treated infants after 7 consecutive days of treatment (0.2 mL every 4 hours x 7 days), compared to placebo controls (p=0.04) but these differences were not sustained, when measured 14 days after the treatments were discontinued. 67 Findings from these four recent studies suggest that an uninterrupted regimen of sustained and prolonged oropharyngeal exposure to protective milk biofactors, until oral feeds of mother's milk are introduced, is more likely to provide sustained immune benefits and impact clinical outcomes.

A significant limitations to published research is the wide variability in methodologies for the dose administered (ranging from 0.1 mL to 1.0 mL), frequency of treatments (every 2 to every 6 hours, also on an 'as needed' basis), duration of treatment (from 2 to 7 days), use of a syringe versus a cotton or foam swab, and the use of fresh versus frozen milk. The percent of 'planned treatments' that were actually given is typically not reported, except for four studies. (58,61,63,65) Also, the procedure for preparation of the 'dose' (ideally in a sterile manner) is usually not described.

In the majority of published studies (85%; 10 out of 12), sterile syringes were utilized to administer the treatments. (56,57,58,61,65-70) Since OPT-MOM is intended as an oral immune therapy, the milk should be treated as a 'medication' with a precise volume drawn up and administered with a sterile syringe. In this manner, appropriate doses of immune and trophic biofactors can be administered consistently with every treatment; as described in prior sections. The use of a swab to administer the milk does not provide a precise dose and is not an evidence-based approach. A cotton swab tends to absorb the majority of the milk, while a (low absorbency) foam swab will not hold and transfer an appropriate amount of milk to the mucosa, because of its low absorbency. Two published studies utilized swabs for the oropharyngeal administration of milk. One study was a feasibility pilot; 63 therefore, the impact of the intervention on immune markers and clinical outcomes for treated infants was not measured. In the second study which utilized swabs, the immune effects of the intervention were not sustained one week after the protocol was completed. (64)

A recently published study defines oropharyngeal administration of colostrum as placing a small amount of colostrum directly onto the oropharyngeal mucosa with a sterile syringe for absorption (67) The OPT-MOM approach incorporates this technique and the use of a syringe facilitates the provision of a consistent dose of biofactors, with every treatment, so that beneficial effects are sustained. The preparation of a batch of syringes using sterile technique, for a 24-hour period of treatments, will promote patient safety.

For OPT-MOM, the use of fresh own mother's milk, administered in the order that it was expressed, is the best approach. Therefore, the infant should receive the colostrum first, with gradual progression to mature milk. In this manner, the ELBW infant will benefit from the natural transition of the milk, which is being administered oropharyngeally, and receive immune benefits similar to those that a breastfed infant would receive.

The use of donor milk for oropharyngeal administration has not been clinically investigated. Importantly, the pasteurization process destroys many immune biofactors or reduces their antimicrobial functions. For example, lactoferrin is reduced by 88%. (76) While donor milk is highly beneficial for ELBW infants, their own mother's milk should be prioritized for oropharyngeal administration. When only a small amount of mother's milk is available post-birth, the donor milk should be used for enteral feeds and the mother's own milk for oropharyngeal administration.

As with any intervention, patient safety and infection control must be prioritized. There have been anecdotal reports of some centers administering fortified breastmilk oropharyngeally to ELBW infants. The infant's nurse collects the 'dose' of milk for oropharyngeal administration at the point of care; when the infant's enteral feeding is due. A small volume of milk is collected (with a syringe or swab) from the aliquot of fortified milk that has been refrigerated and is intended for the infant's enteral feeds. This procedure is repeated every time an enteral feed is administered; between 8 to 12 times per day, depending on the feeding schedule. This practice raises several safety concerns. Repeatedly dipping syringes or swabs, into a container of milk, can potentially contaminate the milk with NICU pathogens; placing the infant at risk for infection. A recent review (79) showed that up to 40% of milk samples in the NICU are contaminated with potential pathogens, (77,78) with the most common organisms being Coagulase- negative Staphylococci, Staphylococcus Aureus, and Enterobacteriaceae. (79) Therefore preventing contamination of mother's milk must be a clinical priority. Another concern is that the milk which is refrigerated in

the NICU and set aside for enteral feeds is typically fortified. There is no evidence to support the safety of administering fortified milk via the oropharyngeal route to ELBW infants <32 weeks CGA. Also the presence of iron-enriched fortifier in oropharygeally-administered mother's milk reduces the immune benefits of the intervention. For example, lactoferrin is a potent biofactor with anti-microbial, anti-inflammatory and immunomodulatory effects. It is protective against L-OS and NEC, (80-83) and may also be protective against VAP, because of its ability to prevent the attachment of pathogens to the oropharyngeal mucosa. Lactoferrin's antimicrobial properties are highly dependent on its ability to compete with bacteria for iron-binding sites. The use of an iron-enriched fortifier reduces lactoferrin's bioactivity since iron-saturated lactoferrin has significantly reduced antimicrobial activity. (84,85) Lactoferrin concentrations are significantly higher in the milk expressed by women who deliver prematurely, compared to milk from mothers who deliver at term. (48,49) Therefore it is important to preserve the potent immune properties of lactoferrin, by using only unfortified milk for oropharyngeal administration and the OPT-MOM procedure.

Admission rates to the NICU (for all birth weight categories) have increased in the U.S. from 64.0 per 1000 live births in 2007 to 77.9 per 1000 live births in 2012 (relative rate, 1.22; 95% CI, 1.21-1.22 [P < .001]).86 While OPT-MOM is primarily intended for the ELBW population, it may be very beneficial for all NICU infants who are unable to feed orally, including VLBW infants, late-preterm infants, and term infants who are unable to breastfeed.

Conclusions

The lack of oropharyngeal exposure to amniotic fluid biofactors, which provide immune protection throughout the last trimester of pregnancy, may increase the risk for prematurity-associated infectious morbidities for the ELBW infant. This deficit may be corrected by utilizing the OPT-MOM approach; a natural alternative to mimic the protective effects of amniotic fluid, until oral feeds can be safely introduced. As a potential adjunctive immune therapy, OPT-MOM requires frequent and sustained treatments administered over several weeks post-birth, with precise dosing of mother's milk. This uninterrupted protocol is more likely to lead to sustained immune benefits and positive health outcomes, for recipient preterm infants, compared to shorter protocols. However, more research is needed, with a consistent methodology, in well-designed, adequately- powered safety and efficacy RCTs. To promote patient safety, strict infection control must be a priority when administering oropharyngeal milk to infants in the NICU; especially when providing this intervention to extremely premature infants.

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