Exclusive human milk (HM) feedings have consistently been shown to improve clinical outcomes in premature infants; these include reduced risks for late-onset sepsis, bronchopulmonary dysplasia, retinopathy of prematurity, and necrotizing enterocolitis, along with improved neurodevelopment.[1-4] As healthcare professionals caring for premature infants, our priorities are to optimize their health, immunity, and growth. The use of HM feedings can achieve these priorities by providing: 1) well balanced highly bioavailable macro- and micronutrients; 2) immunomodulatory molecules that either provide direct substitutive immunity (e.g. sIgA, lactoferrin, and antioxidants) or promote immune development of the infant (e.g. TGF-β); 3) prebiotics (e.g. HM oligosaccharides); and 4) probiotics (e.g. HM microbiota).[5] All the aforementioned HM components work in concert to create the most desirable environment within the recipient infant to optimize growth and development. As the HM literature has advanced exponentially to show superiority of HM feedings over the use of formula, the use of donor human milk (DHM), when mother's own milk (MOM) is inadequate or not available, has risen rapidly in neonatal intensive care units (NICU) around the globe.[6]

Processing techniques are required for all donated HM to eliminate potential pathogens.[6] However, the biggest challenge is to maximize retention of the beneficial HM components to still optimize growth and development in the recipient infant. Currently, the most common processing technique used by HM banks worldwide is the holder pasteurization technique. The holder pasteurization process is a low heat method, with pooled milk warmed to 62.5°C and held for 30 minutes prior to rapid cooling and subsequently frozen until used. In the study by Lima et al. in this issue of the *Journal of Pediatric Gastroenterology and Nutrition*, the authors compared the holder pasteurization

technique to a less commonly used process, retort processing, found to be used in some hospital settings.[7] The retort process is an ultra high heat (121°C for 5 minutes), combined with high-pressure (15 psi), sterilization technique originally invented to produce shelf stable foods as an alternative to canning. It has been widely used by the U.S. military and has recently regained popularity in the oral nutrition supplement market. Only one other study by Meredith-Dennis et al. has been published to compare HM component retention between these two methods.[8] The combined results from these two studies revealed that the holder technique retains more lactoferrin, IgA, and lysozyme; whereas macronutrients and HMO contents were similar between the two methods. Lima et al. also found that lysine and thiamine concentrations were significantly reduced by the retort technique compared with the holder technique. Based on the results of these two studies and the limited HM components measured by these investigators, it appears that the current most commonly used method of holder pasteurization technique retains more beneficial HM components.

It is important to mention here that while these two studies showed that one DHM processing technique preserves more of select few HM components than the other, there are hundreds more beneficial HM components that have not been measured as a result of processing techniques. When thinking about feeding prescriptions for the premature infant, we must consider everything that contributes toward growth and development. It is simply not adequate to only think in terms of macronutrient contents of DHM vs. MOM to support energy balance. The gastrointestinal (GI) tract of the premature infant does not yet produce optimal quantities of digestive enzymes, and MOM provides such enzymes that help the infant maximize absorption of macronutrients.[9] We know that heat

in general causes conformational changes in protein structures leading to denaturation and loss of activity, which has profound implications in both DHM processing techniques translating to decreased or complete loss in enzymatic activities. A number of HM growth factors support maturation and development of the infant's GI tract and immunity, as well as overall growth, many of which are also protein molecules that can be abolished during the heating process. Lima et al. measured thiamine concentration as a representative of water-soluble vitamins in HM; however, it is difficult to extrapolate one single vitamin to represent a wide array of other micronutrients in HM. Furthermore, premature infants have decreased redox system to protect themselves from excess oxidative stress often experienced during the birthing process, as well as various NICU interventions. Antioxidants in HM are especially important in premature infants to offset their reduced redox system and mitigate any direct oxidative damage.[10] Additionally, antioxidants are known to protect macromolecules such as lipids from oxidation[10]; lipids in particular are essential for development of the brain and retina photoreceptor membranes. Antioxidants in general are especially sensitive to heat, thus likely reduced, if not completely lost during these processing techniques.

Aside from the HM components lost during processing techniques, clinicians often prescribe additional nutrient supplementation to DHM feedings to support growth due to observations of slowed growth with DHM. As an astute clinician, one must bear in mind both the HM components described above (e.g. digestive enzymes), and physiology of the premature GI tract. DHM will provide reduced amounts of digestive enzymes and growth factors. Simply providing additional macronutrients as supplementation does not necessarily translate to proportional increased absorption of such nutrients. Protein, as an

example, is the most commonly prescribed additional supplementation to promote growth. When excess unabsorbed protein (either intact or peptides) make way into the colon, it serves as major fuel for potentially harmful putrefactive bacteria. Putrefactive bacteria have been shown to produce metabolites that are detrimental to colonocytes and increase risk of colonic inflammation.[11]

To conclude, while DHM is the best alternative when MOM is inadequate or not available, the number one priority for NICU clinicians and institutions should be to optimize support for mothers to provide MOM. The comprehensive profile of HM components in MOM works in concert to support the premature infant's growth and development. While one DHM processing technique may retain more HM components than the other, processing techniques in general will profoundly reduce majority of these vital HM components, thus diluting the overall protective effects of HM feedings.

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