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Human milk is the feeding strategy to prevent necrotizing enterocolitis!

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ABSTRACT

Human milk is the preferred diet for preterm infants as it protects against a multitude of NICU challenges, specifically necrotizing enterocolitis. Infants who receive greater than 50% of mother's own milk (MOM) in the 2 weeks after birth have a significantly decreased risk of NEC. An additional factor in the recent declining rates of NEC is the increased utilization of donor human milk (DHM). This creates a bridge until MOM is readily available, thus decreasing the exposure to cow milk protein. Preterm infants are susceptible to NEC due to the immaturity of their gastrointestinal and immune systems. An exclusive human milk diet compensates for these immature systems in many ways such as lowering gastric pH, enhancing intestinal motility, decreasing epithelial permeability, and altering the composition of bacterial flora. Ideally, preterm infants should be fed human milk and avoid bovine protein. A diet consisting of human milk-based human milk fortifier is one way to provide the additional nutritional supplements necessary for adequate growth while receiving the protective benefits of a human milk diet.

Introduction

The challenge of meeting the nutritional goals of the extremely preterm (EP) infant while attempting to avoid serious complications and adverse outcomes such as necrotizing enterocolitis (NEC) can be met by a feeding strategy comprising human milk.[1,2] Such a diet meets nutritional needs as well as provides significant health benefits to the recipient. Overall, the rates of NEC have been declining in EP infants, most likely a result of the increased utilization of human milk, including donor human milk. This review focuses on a description of the beneficial effects of a human milk diet and the role of donor human milk to understand the specific protective effects of these diets against NEC.

Clinical studies with MOM

Mother's own milk (MOM) provides significant benefits for the EP infant. These include prevention of infection-related events such as urinary tract infection, NEC, and sepsis, and shortens the length of stay in the NICU.[3–6] Beneficial effects of such a diet extend beyond the neonatal period as measured by fewer hospitalizations for respiratory illness up to 3 years of age.[7] The overall re-admission rate for infectious disorders decreased by 5% for every 10 mL/kg/day of human milk received during the NICU stay.[7]

There is a 50% reduction in the rate of NEC and/or late-onset sepsis and a shortened length of hospital stay among the EP infants receiving MOM at an average daily dose of

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more than 50 mL/kg compared to MOM + formula, or formula alone.[3] That observation suggested that the dose of MOM (more than approximately 50 mL/kg/day) was important to detect a beneficial health effect in EP infants.[3] The concept of a "dose-dependent" protective effect of human milk has been reported elsewhere. When receiving a diet of more than 50% MOM in the first 14 days after birth, infants had an 83% reduction in the subsequent development of NEC compared to those receiving a diet of less than 50% MOM.[8] Even earlier initiation of MOM, days 1–5, at a dose of >50% of enteral intake, is associated subsequently with a lower incidence of NEC, sepsis, and/or death during the first 60 days after birth.[9] An even stronger prediction model was observed if the intake of MOM was more than 50% during days 6–10 after birth.[9] A daily intake of more than 50 mL/kg for 4 weeks also is associated with a lower rate of neonatal sepsis.[10]

While the daily dose of 50 mL/kg/day is required to detect a difference in health benefits, this amount should not be the ultimate goal. In a retrospective analysis of 1272 infants, the likelihood of NEC or death after 14 days was decreased by a factor of 0.83 for each 10% increase in the proportion of total intake as human milk, illustrating the importance of a predominantly human milk diet.[11] In a case–control study of 1028 EP infants comparing those who developed NEC with matched controls, there was a fourfold increased risk of NEC if the infants had received MOM for less than 7 days.[12] This illustrates the minimum days of MOM necessary to provide a protective effect against NEC. These studies suggest that in the EP population, the important early protective effects of a human milk diet are long-lasting. The beneficial effects extend beyond protection from infection-related disorders. Human milk-fed preterm infants have greater odds of developing bronchopulmonary dysplasia and retinopathy of prematurity if their diet is formula or mixed feeding compared with exclusive human milk.[13] Human milk feeding protects against retinopathy of prematurity and its most severe form leading to retinal detachment.[14,15] These observations support a role of human milk as an antioxidant as well as containing factors that affect angiogenesis.

Human milk is tolerated better by preterm infants due to its effects on the gastrointestinal tract. Specifically, when advancing feeds, there are fewer gastric residuals and less feedings withheld when compared with formula feeding.[3] Furthermore, the time to achieve full feeds is almost double when the percentile of human milk intake is less than 20% compared with a diet of more than 80% human milk.[16]

Clinical studies with donor human milk

Mothers of EP infants may not be able to provide adequate volumes of milk to meet their infants' needs. A study of EP infants identified that, only 30% of mothers were able to meet their infants' needs for feeding throughout the hospitalization in the NICU.[5] Donor human milk (DHM) has become more available in NICUs to enable an exclusively human milk diet for the EP infant.[17] In the NICU, DHM acts as a bridge until MOM production meets the infant's needs and also results in an enhanced MOM production.[18] In a multicenter investigation, the use of DHM was associated with a 10% increase in the rate of MOM utilization and a 2.6% decrease in the rate of NEC.[19]

DHM is not the same as MOM. DHM must be pasteurized, stored, and mixed. Since human milk is not homogenized, and when DHM interfaces with many containers, there is a significant loss of fat. DHM generally is donated later in lactation by women delivering at term, which means that the milk contains less protein, electrolytes, and trace elements than fresh milk. Indeed, the macronutrient contents of milk donated to a milk bank varies widely.[20] In addition, there is significant variability in immunoactive factors after pasteurization. Clinical reports on the use of DHM suggest that infants fed such a diet have poor growth and nutritional inadequacies but significantly less NEC and better feeding tolerance.[21]

The first randomized, controlled trial of DHM was conducted in 210 EP infants who were assigned to receive DHM or preterm formula if their MOM supply was inadequate.[5] Thus, diets of fortified DHM and preterm formula were fed as supplements to a diet of fortified MOM. A parallel group receiving only fortified MOM served as a reference. The major outcome of the trial, the combined rate of sepsis and/or NEC, was similar between the two groups fed DHM or formula (40%) compared with the reference group fed MOM (20%). A potential explanation for the lack of protection from a fortified DHM diet may be the lesser immune protection from pasteurized milk coupled with the use of bovine-based fortifiers containing intact protein. Intact bovine milk protein may induce intestinal inflammation that is not mitigated by a pasteurized donor milk diet.[22,23]

A multicenter randomized trial in EP infants studied the effects of an exclusive human milk diet (that avoided intact cow milk protein and other bovine milk attributes) comprising MOM with fortifier derived from human milk and pasteurized DHM if MOM was unavailable.[24] This diet group was compared to a group receiving MOM fortified with bovine-derived fortifier (made with intact bovine protein) and preterm formula if MOM was unavailable. The rates of NEC and NEC requiring surgery were markedly lower in the exclusive human milk group. A subsequent small randomized trial enrolling infants whose mothers did not provide their milk reported very similar outcomes, fewer parenteral nutrition days, and less NEC and NEC requiring surgery, compared to similar infants receiving preterm formula.[25] They demonstrated that for every 10% increase in milk intake of anything other than MOM, the risk of NEC increased by 21%.[26] Of the more than 200 infants studied, the summary data indicate that infants fed an exclusive human milk diet have lower mortality, and less NEC and less NEC requiring surgery, when compared with a diet containing bovine-based products.[26]

Confirmation of these data recently has been reported from a retrospective review of more than 1500 EP infants fed an exclusive human milk diet or a diet containing bovine-based products.[27] In addition, a review of EP infant feeding found more recent use of both MOM and DHM and these diets were associated with lower rates of NEC, better feeding tolerance, shorter duration of hospital stay, and reduced hospital costs.[28,29] Thus, the data support the use of an exclusive human milk diet for the EP infant, but the role of intact protein is unanswered.

Human milk ideally protects against NEC

Preterm infants have altered host defenses that increase their susceptibility to NEC.[30] Their gastrointestinal tract