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Human Milk is the Feeding Strategy to Prevent Necrotizing Enterocolitis

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Abstract The use of human milk in the neonatal intensive care unit clearly has short and long-term beneficial effects, but its role in the prevention of necrotizing enterocolitis (NEC) cannot be understated. Immaturity of the intestinal tract, barrier function, and mucosal defense contributes to NEC. Human milk feeding enhances maturity of the intestinal tract, barrier functions, and mucosal defenses by providing components such as immunoglobulin A, lactoferrin, lysozyme, oligosaccharides, epidermal growth factor, acetylhydrolase, erythropoietin, arginine and glutamine, and polyunsaturated fatty acids, and the ability to promote a commensal intestinal microflora.

Keywords Human milk · Donor human milk · Necrotizing enterocolitis

Introduction

The challenge to meet the nutritional goals of the extremely low birth weight (ELBW) infant while attempting to avoid serious complications and adverse outcomes such as necrotizing enterocolitis (NEC) can be overcome with human milk [1, 2]. Such a diet meets nutritional needs as well as provides health benefits to the recipient. Why a human milk diet particularly benefits the health of the ELBW infant will be reviewed.

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Mother's Own Milk

It has been demonstrated that a mother's own milk (MOM) diet is beneficial for ELBW infants because it is associated with prevention of late onset sepsis (LOS), NEC, and urinary tract infection [3–7]. That the host protection extends beyond the NICU stay is evidenced by fewer readmissions to the hospital for respiratory illness through almost 3 years [8]. It is estimated that there is a 5 % decrease in the odds of being re-hospitalized for any infectious disease for every 10 mL/kg/day human milk consumed in the NICU [8].

There is a 50 % reduction in the rate of NEC and/or LOS and a shortened length of hospital stay among the ELBW infants receiving MOM at an average daily dose of 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 ELBW infants [3].

The concept of a "dose-dependent" protective effect of human milk has been reported elsewhere. ELBW infants ($n = 202$) receiving more than 50 % MOM in the first 14 days after birth had an 83 % reduction in the subsequent development of NEC compared to those receiving a diet of less than 50 % MOM [9]. A daily intake of more than 50 mL/kg for 4 weeks also is associated with a lower rate of neonatal sepsis [10]. The dose-dependent benefit should not be considered maximized at 50 % intake. In a large retrospective analysis of 1,272 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, suggesting the importance of dose and the predominance of a human milk diet [11].

Early initiation of human milk is advocated and practiced in the NICU. A Dutch study of 349 infants observed that the intakes of MOM >50 % during the first 5 days after birth was associated subsequently with a lower incidence of NEC, sepsis, and/or death during the first 60 days after birth [6]. An even stronger prediction model was observed if the intake of MOM was more than 50 % during days 6–10 after birth [6]. These studies suggest that in the ELBW population the important early protective effects of a human milk diet are long-lasting.

There are effects of human milk on the gastrointestinal tract of ELBW infants that account for the better acceptance of this milk when compared to formula. There are significantly fewer gastric residuals and less time feedings were withheld in infants receiving MOM versus formula [3]. Milestones, such as achievement of full enteral feeding and length of hospital stay, are significantly shortened with the feeding of MOM. These milestones are achieved in nearly twice as many days when the percentile of human milk intake was less than 20 % as compared to more than 80 % [12].

Human milk feeding in ELBW infants also has been shown to protect against retinopathy of prematurity and, its most severe form, retinal detachment [13, 14]. These observations support a role of human milk as an antioxidant as well as containing factors that affect angiogenesis.

Pathogenesis of NEC

Clinical studies demonstrate that human milk protects the ELBW infant from NEC. To understand this relationship, it is important to describe a general overview of the pathogenesis of NEC. The etiology of NEC is unknown, but it is probably caused by multiple factors in a presumably genetically susceptible host. Factors implicated in its pathogenesis include prematurity (immature intestinal function), milk feeding (substrate), microbial colonization, impaired mucosal defense, and to some degree, circulatory instability. These factors act together to cause mucosal injury, which appears to be the initial event [15–17].

Bacterial colonization plays a pivotal role in the pathogenesis of NEC. Colonization of the normal GI tract occurs rapidly after delivery. The normal colonization is altered by the NICU environment. Immature intestinal motility predisposes to bacterial overgrowth which is unchecked due to the coexistence of an immature mucosal host defense. Increased gastrointestinal permeability potentiates bacterial translocation. Intestinal signaling becomes disrupted. Thus, these factors support and promote the invasion of pathogenic organisms into the circulation and set up an immune activation with an intense intestinal inflammatory response.

Contributing to the pathogenesis of NEC, milk feeding serves as a substrate for bacterial proliferation in the gut. Organic acids, short chain fatty acids, carbon dioxide, and hydrogen gas are produced by bacterial fermentation milk component nutrients. These products of fermentation may be toxic to intestinal epithelium and increase intestinal distention. In animal studies using an intestinal loop model, addition of casein creates a favorable milieu for infiltration of cellular elements and vasoactive compounds, leading to mucosal injury [18].

Table 1 Factors in human milk reported to enhance protection from necrotizing enterocolitis

Oral IgA-IgG [28]
PAF acetylhydrolase [29]
Long-chain polyunsaturated fatty acids [30]
Erythropoietin [31]
Arginine and glutamine supplementation [32]
Epidermal growth factor [19]
Probiotics [33–35]
Lactoferrin [36]
Oligosaccharides [20•]

Human Milk is Protective

Preterm infants are susceptible to the development of NEC because immunologic and gastrointestinal immaturity result in altered host resistance. Mucosal defense in the intestinal tract is mediated by several interrelated components. Factors that contribute to innate resistance include luminal pH, enzymes, mucins, epithelial barriers, and gut motility, as well as nonspecific antimicrobial factors such as lactoferrin and lysozyme. Factors present in human milk play a protective role by reducing inflammation and the subsequent invasion of pathogenic bacterial species in the gastrointestinal tract (Table 1). These factors include the enzyme platelet activating factor (PAF) acetylhydrolase, which blunts the immune activation sequence promoted by PAF. The local host defenses are enhanced by the addition of secretory IgA, lactoferrin, lysozyme, and cytokines (IL-10, IL-11) from human milk. Components in human milk, such as epidermal growth factor, nucleotides, and glutamine also stimulate intestinal maturity [19]. Human milk antioxidants, such as vitamin E, carotene, and glutathione, also reduce oxidative stress.

Immaturity of the gastrointestinal tract, including luminal function, motility, increased permeability, and barrier function, and diminished mucosal enzymes and GI

trophic hormones, such as proteases and pepsin, and increased gastric pH, also predispose the preterm infant to NEC [11].

Human milk oligosaccharides (HMO) are long-chain sugars, more than 150 such compounds that represent the third most prevalent constituent in human milk. HMOs are prebiotic agents that presumably act by enhancing proliferation of bifidobacteria and prevent of adhesion of pathogenic bacteria. In animal models studied under conditions that produce NEC, the HMOs are found to prevent intestinal injury compared to synthetic oligosaccharides. Indeed, human milk diets and formula diets that were supplemented with HMOs prevent intestinal injury while diets of formula with or without synthetic oligosaccharides fail to prevent intestinal injury in the model [20•]. The science of HMOs as luminal protective agents is intriguing.

Probiotics reduce NEC in neonates because they improve the intestinal barrier function, modulate the immune system, suppress the growth or epithelial binding and invasion, of pathogenic bacteria. It is likely that probiotics provide commensal bacterial colonization similar or additive to that promoted by human milk.

The Table 1 lists several components in human milk that in clinical and animal models employing individual components have been associated with protection from NEC.

Donor Human Milk

Mothers of ELBW infants may not be able to supply 100 % of their infants' needs for MOM. One study of ELBW infants observed that only 30 % of mothers were able to provide 100 % of the milk for their ELBW infant [7]. Donor human milk (DM) has been considered an alternative to MOM and there has been an increase in the availability of DM in the recent years [21, 22]. It has been shown that DM (vs formula) provides a protective effect against NEC and enhanced feeding tolerance in preterm infants [23]. However, DM has been associated with protein and mineral deficiencies and slower growth in preterm infants [23].

A randomized controlled trial to determine if DM is a suitable proxy to MOM was conducted in 210 infants, approximately 28 week gestation and with birth weights of approximately 1,000 g [7]. Infants were assigned to receive either DM or formula as supplements if their MOM volume was insufficient. The study found that the rates of sepsis and/or NEC were similar in infants who received DM or preterm formula as supplements to MOM. The infants who continued to receive MOM had a 50 % reduction in these outcomes. A possible explanation of these findings may relate to the bovine milk protein components of the human milk fortifiers used in the human milk groups. There is speculation that cow milk protein induces inflammation that is counteracted by the host defense properties of MOM, but these same properties are inadequately preserved after pasteurization [18, 24]. Thus, the infant fed bovine milk-based preparations with DM may be inadequately protected [7].

These observations prompted the investigation of an exclusive human milk diet (human milk-based human milk fortifier and DM if MOM was unavailable), appropriately fortified to meet the needs of the ELBW infant [25, 26]. A multicenter randomized trial in ELBW infants (mean birth weight 900 g, gestational age 27 weeks) reported significantly lower rates of NEC and NEC requiring surgery in infants receiving the exclusive human milk diet than those receiving MOM with bovine-based human milk fortifiers and bovine-based formula if no MOM was available [25]. A further study in ELBW infants whose mothers were unable or unwilling to provide MOM identified similar benefits from an exclusive human milk diet than from formula [26]. That study also found markedly less need for parenteral nutrition in the group receiving an exclusive human milk diet. The investigation determined that six infants needed to be treated with an exclusive human milk diet to prevent one case of surgical NEC. To date, an exclusive human milk diet versus a diet containing bovine milk-based products has been studied in 260 ELBW infants [27••]. The summary data find that infants fed an exclusive human milk diet have lesser mortality (2 %), NEC (5 %), and NEC surgery (1 %) than those receiving a diet containing bovine milk-based products (8, 17, and 12 %, respectively) [27••].

Conclusion

These data support recommendations of the American Academy of Pediatrics that encourage the use of MOM for all very low birth weight infants and DM if MOM is unavailable [2]. Although this recommendation is made to preclude the use of bovine milk-based formula in the preterm infant population, there remain no data that compare exclusive MOM versus exclusive DM. Given that newer human milk fortifiers not containing intact bovine protein are available, the possibility of such a future study can be considered. However, it is doubtful that an exclusive DM diet will be more beneficial than exclusive MOM.

Disclosure Richard J. Schanler declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies on animal subjects performed by the author. The clinical studies cited in this article that were performed by the author had the approval of the Institutional Review Board for Human Subjects Research at the appropriate institutions.

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