Overview: The Clinical Perspective\textsuperscript{1,2}

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The recommendation to feed term infants human milk, based on the nutritional benefits, contributions to host defense and gastrointestinal growth, as well as psychological benefits of maternal-infant bonding, has been extended to the premature infant (American Academy of Pediatrics and Work Group on Breastfeeding 1997). Human milk may be of special benefit to the premature infant because of the interrelationships among nutritional support, gastrointestinal maturity and host defense. In particular, the high rates of infection and sepsis in the immunosuppressed premature infant are the direct results of exposure to the numerous pathogens in the nursery environment. In addition, circulatory instability and apnea are common factors that are thought to interact with feeding and bacterial colonization to contribute to the development of necrotizing enterocolitis (NEC)\textsuperscript{3}. Thus, by incorporating both nutritional and host defense benefits, human milk may protect the premature infant.

A recent report from the National Institute of Child Health and Human Development Neonatal Research Network (Stoll et al. 1996) indicated the importance of the problem of late-onset sepsis in premature infants and its association with NEC, commenting that these conditions accounted for major morbidity and mortality, prolonged hospitalization and tremendous economic burden. Of note was the variation in incidence among the 12 centers in the Network, but no data were provided on the use of human milk in the nurseries at the study sites. Efforts directed at partially reducing the incidence of these medical conditions, potentially through the feeding of human milk, therefore, would significantly affect the cost of medical care (Gaynes et al. 1996, Kliegman et al. 1993, Stoll et al. 1996).

\textbf{Human milk and host defense in premature infants}

Specific bioactive factors in human milk, such as secretory immunoglobulin A (sIgA), lactoferrin, lysozyme, cytokines, oligosaccharides, enzymes and cellular components, may affect the host defense of the infant (Gauld et al. 1977, Goldblum and Frawley 1996, Hambraeus et al. 1977, Lindblad et al. 1978, Newburg 1996, Raitha et al. 1976, Rassin et al. 1977, Telemo and Hanson 1996), but the specific mechanism(s) for this protection is unclear. One investigation reported a decreased incidence of NEC in premature infants fed a preparation of immunoglobulins (Ig) A and G derived from serum (Eibl et al. 1988). The infants fed the IgA-IgG also had a significantly higher fecal excretion of immunologically active IgA than control infants, suggesting a local protective effect throughout the gastrointestinal tract. In our studies at the Children’s Nutrition Research Center, we demonstrated greater fecal and urinary IgA and lactoferrin excretion in premature infants fed human milk vs. formula (Goldblum et al. 1989, Schanler et al. 1986). Further studies in our Center indicated that human milk–derived lactoferrin was absorbed intact and excreted in the urine of premature infants, suggesting local as well as systemic action (Hutchens et al. 1991). Nonrandomized clinical studies report a lower incidence of a variety of infections in premature infants fed human milk, regardless of whether the milk was fresh, frozen, pasteurized or co-administered with formula (Contreras-Lemus et al. 1992, El-Mohandes et al. 1995, Hylander et al. 1998, Narayanan et al. 1980, 1983 and 1984). The devastating acute gastrointestinal inflammatory disease in premature infants, NEC, is reportedly a less frequent occurrence when the prior diet was human milk compared with formula or no milk (Yu et al. 1981). Lucas and Cole (1990) reported a markedly lower incidence of NEC in a large nonrandomized study of hospitalized premature infants fed human milk exclusively or partially, compared with formula only. That study reported clinical cases as well as confirmed cases (via surgical or autopsy specimen); in both circumstances, the incidence of NEC was significantly lower in premature infants fed human milk, even if they received supplements of donor human milk or formula.
Because that study was conducted in the early 1980s, the infants received only unfortified human milk. A follow-up randomized trial investigated the incidence of sepsis and NEC in premature infants fed multinutrient-fortified human milk compared with partially supplemented human milk (containing only additional phosphorus, sodium and vitamins) (Lucas et al. 1996). The study was complicated by the large quantity of preterm formula given to infants because of poor maternal milk production (Schanler 1996). Thus, the study was unable to evaluate exclusive human milk feeding. The study reported no significant differences in the incidence of sepsis or NEC. However, when both outcomes were grouped together (sepsis plus NEC), the infants fed multinutrient-fortified human milk had a greater incidence of the combined morbidities than the infants fed partially supplemented human milk. It is difficult to draw specific conclusions regarding the risks of sepsis and NEC from that investigation until a confirmatory investigation of exclusive fortified human milk feeding or a dose-response evaluation is conducted.

A recent investigation of feeding strategies in premature infants (time of initiation, method of tube-feeding and type of milk fed) is pertinent to the above observations (Schanler et al. 1999b). Of all of the strategies investigated, the study outcomes were most affected by the type of milk fed, specifically, the quantity of human milk received. The average (and cumulative) intake of human milk (predominantly fortified human milk) was associated significantly with less need for parenteral nutrition; more rapid attainment of complete tube-feeding; better feeding tolerance; lower incidence of positive blood cultures, late-onset sepsis episodes and NEC, less need for antibiotics; and a shorter duration of hospitalization (Schanler et al. 1999a). Late-onset sepsis and NEC occurred in 31 and 2%, respectively, of infants fed predominantly fortified human milk compared with 48 and 13%, respectively, in infants fed preterm formula. The study also reported that the more human milk consumed, the lower the number of episodes of late-onset sepsis and/or the number of positive blood cultures (Schanler et al. 1999a). These results differ from the multicenter study of fortified vs. partially supplemented human milk by such a magnitude that further investigations are mandated.

**Intestinal responses to feeding**

Studies of gastrointestinal priming with milk suggest that even when feeding small volumes of milk, significant trophic hormone responses are elicited in premature infants (Lucas et al. 1986). Feeding premature infants (gestational age 28 wk, birth weight ~1 kg) small volumes of milk, ~20 mL/(kg·d), beginning at 4 d of age appears to stimulate endogenous lactase activity, which remains greater until d 50 compared with that of infants receiving only parenteral nutrition for 14 d (Shulman et al. 1998a). Human milk increases the effect of milk on endogenous lactase activity (Shulman et al. 1998a). Gastrointestinal permeability also appears to be affected by human milk. Premature infants, ~28 wk gestation with birth weights of ~1 kg, have lower permeability than infants fed formula (Shulman et al. 1998b). Postnatal age and the receipt of glucocorticoids antenatally enhance the effect of human milk on gastrointestinal permeability (Shulman et al. 1998b). Thus, human milk may modify the gastrointestinal tract in such a way that the barrier to infectious agents is protected.

**SUMMARY**

It is apparent that human milk has a protective effect on premature infants, who benefit from a reduced incidence of infection and NEC. Both entities are associated with immaturity of the gastrointestinal tract. The modifying effects of human milk on the premature infant's gastrointestinal tract are important and comprise the subject of the following reports.

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**LITERATURE CITED**


