

Lactoferrin Supplementation and Its Gut Health Benefits

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Expanded Commentary from the Faculty

Lactoferrin is a major constituent of the whey protein fraction in human breast milk and other secretory fluids. This is a multifunctional protein that binds and transports iron, has bacteriostatic and bactericidal properties, is immunomodulatory and anti-inflammatory, and promotes maturation of the infant gut. Although lactoferrin is present in bovine milk, and structurally similar to human lactoferrin, human breast milk has 4-30 times more lactoferrin than bovine milk, and is most abundant in colostrum.

As a component of breast milk, lactoferrin has several important properties that suggest supplementation of formula with lactoferrin would be beneficial. The ability of lactoferrin to bind and sequester free iron, results in bacteriostatic activity, and lactoferrin and lactoferrin-derived peptides (eg, lactoferricin) have multiple bactericidal mechanisms. Lactoferrin may also supply beneficial microorganisms with iron, thereby promoting their growth. Gut enterocytes bind lactoferrin, leading to increased enterocyte proliferation and differentiation, which may consequently affect mucosal permeability and intestinal maturation.¹ Lactoferrin also reduces the production of inflammatory cytokines and affects the balance of Th1:Th2 cells.²

In clinical trials, supplementing infants' diets with bovine lactoferrin has had an effect on the prevention of sepsis, necrotizing enterocolitis (NEC), and respiratory infections. Very low-birth-weight infants who received lactoferrin, with or without *Lactobacillus* GG, had a lower incidence of late-onset sepsis, and also had a lower risk of NEC and mortality.^{3,4} King et al also showed that supplementing bovine-based formula with lactoferrin reduced the incidence of lower respiratory tract infections and improved hematocrit levels in preterm infants.⁵

Considerations for lactoferrin supplementation:

- Start lactoferrin supplementation early^{3,6}
- Add lactoferrin at ≥ 100 mg/day, and consider adding a probiotic
- Lactoferrin supplementation is less effective in larger or term neonates⁶

While initial studies of lactoferrin suggest that supplementation can improve outcomes in preterm or formula-fed infants, there are several questions that need to be resolved. The ideal dose and dosing regimen of lactoferrin is unknown. At least 100 mg/kg/day is probably a minimum, and preterm infants may benefit from prolonged lactoferrin supplementation.⁷ Probiotic supplementation also seems to be important, but the best combination and selection of probiotics has not yet been defined. Neither has the safety of lactoferrin, although bovine lactoferrin has been designated as generally regarded as safe (GRAS) by the FDA. Finally, a recombinant, human lactoferrin, talactoferrin, is available, but the effectiveness of this form of lactoferrin as a supplement still needs to be established.⁸

Group Discussion Items

- What is our hospital's protocol for lactoferrin supplementation, including preparation, handling, and storage?
- Discuss strategies for improving our fortification practices, particularly for preterm and term neonates who are intolerant to feedings.
- Does this information reinforce our current practice?
- If we were to implement or adopt this clinical pearl, what would we do first?
- What other approaches could be used?
- What are the barriers to adopting this clinical pearl in our institution?
- Are there other problems we haven't talked about?

Suggested Readings and Resources

1. Buccigrossi V, de Marco G, Bruzzese E, et al. Lactoferrin induces concentration-dependent functional modulation of intestinal proliferation and differentiation. *Pediatr Res*. 2007;61:410-414.
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3. Manzoni P, Rinaldi M, Cattani S, et al. Bovine lactoferrin supplementation for prevention of late-onset sepsis in very low-birth-weight neonates: a randomized trial. *JAMA*. 2009;302:1421-1428.
4. Manzoni P, Meyer M, Stolfi I, et al. Bovine lactoferrin supplementation for prevention of necrotizing enterocolitis in very-low-birth-weight neonates: a randomized trial. *Early Hum Dev*. 2014;90(Suppl 1):S60-S65.
5. King JC, Cummings GE, Guo N, et al. A double-blind, placebo-controlled, pilot study of bovine lactoferrin supplementation in bottle-fed infants. *J Pediatr Gastroenterol Nutr*. 2007;44:245-251.
6. Ochoa TJ, Zegarra J, Cam L, et al. Randomized controlled trial of lactoferrin for prevention of sepsis in Peruvian neonates less than 2500 g. *Pediatr Infect Dis J*. 2015;34(6):571-576.
7. Kaufman DA. Lactoferrin supplementation to prevent nosocomial infections in preterm infants. *JAMA*. 2009;302:1467-1468.
8. Sherman MP, Adamkin DH, Niklas V, et al. Randomized controlled trial of talactoferrin oral solution in preterm infants. *J Pediatr*. 2016;175:68-73.