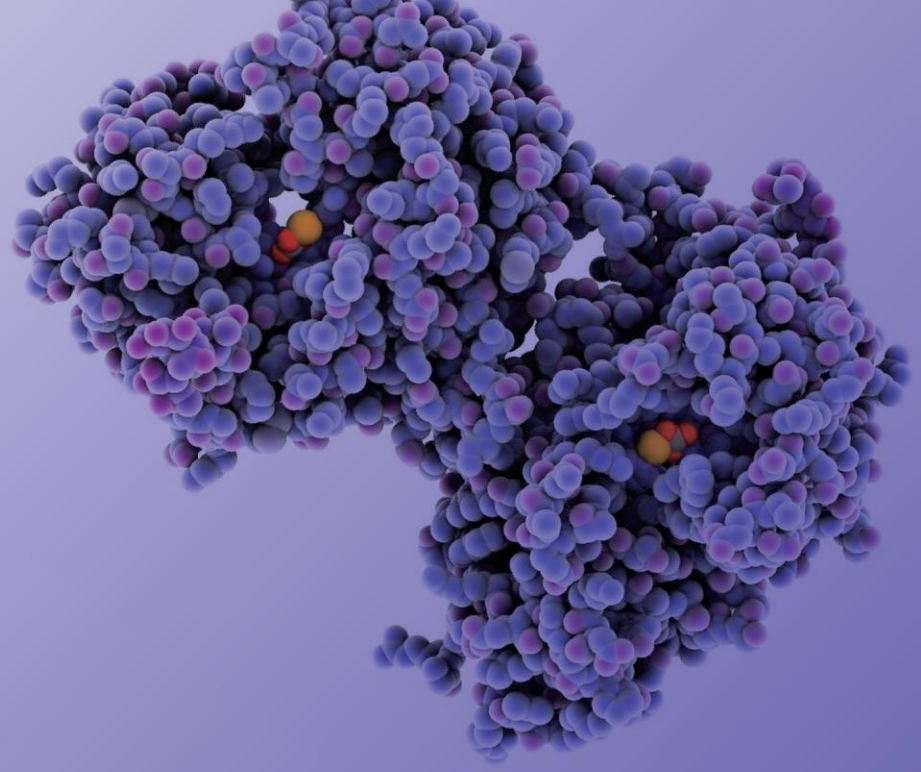
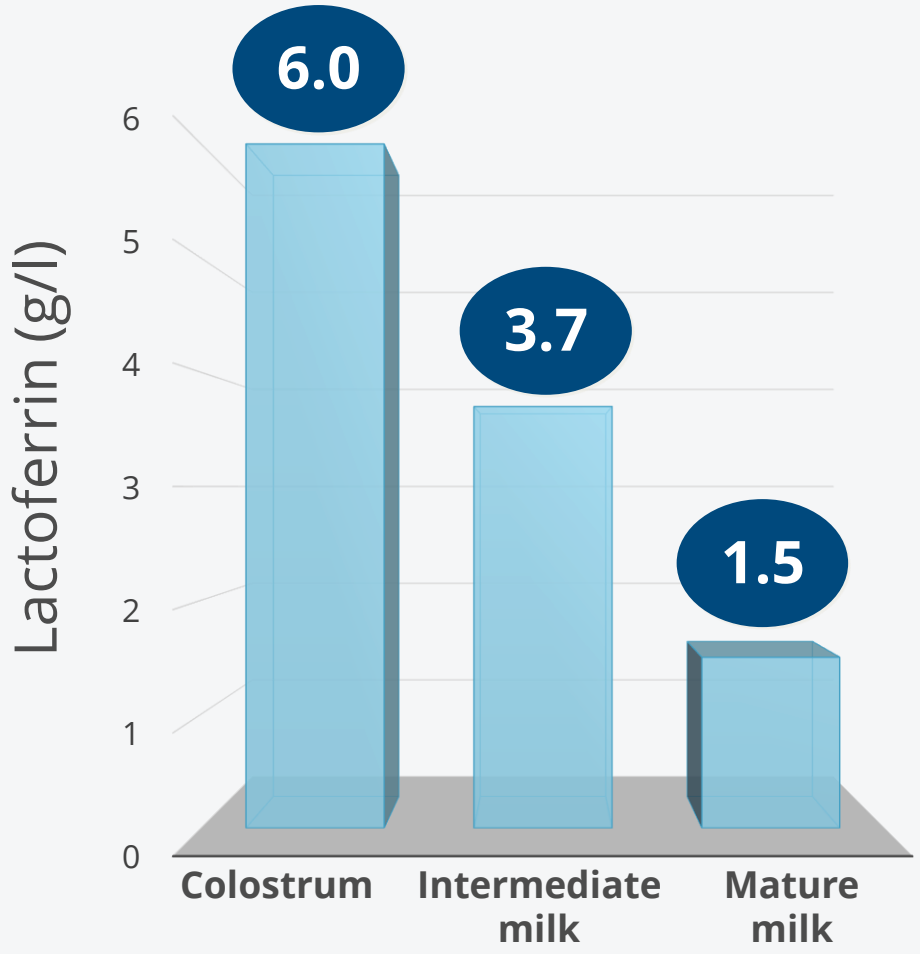


What effect does lactoferrin have on intestinal mucosa development and the health of a newborn?

Lactoferrin Concentration Decreases in Mature Human Milk vs Colostrum



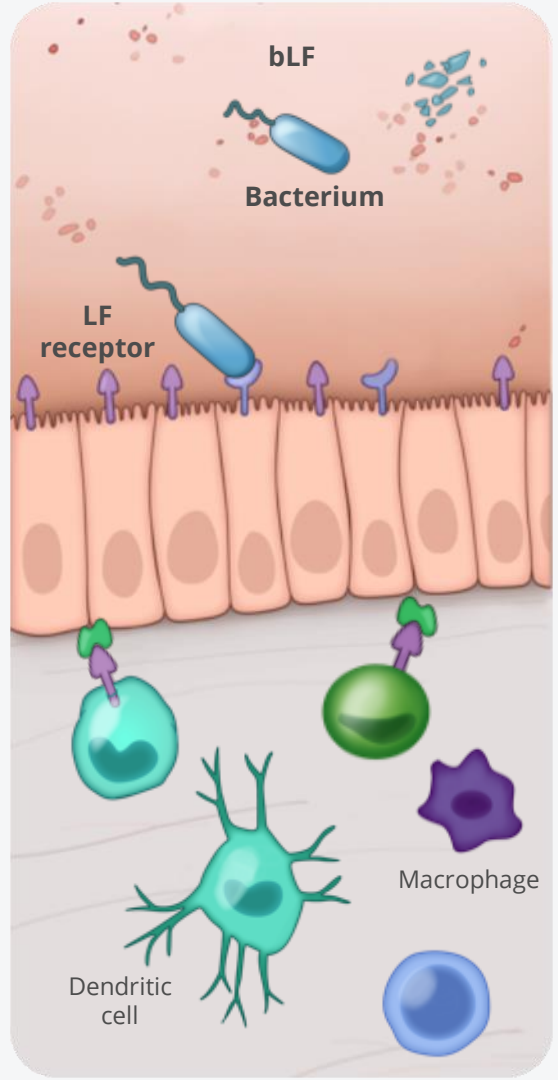
This decrease typically occurs in all mammals.

Milk	Concentrations of lactoferrin
Woman	2 (mature milk) – 6 (colostrum) mg/ml
Cow	0.2–0.5 mg/ml
Rat	<50 mcg/ml
Rabbit	<50 mcg/ml
Dog	<50 mcg/ml
Goat	0.2 mg/ml
Pig	0.2 mg/ml

Albenzio M, et al. *Am J Perinatol*. 2016;33(11):1085-1089.

Functions of Lactoferrin in Gut Development and Immune Defense

- **Intestinal development**
  - Promotes cell proliferation and differentiation
  - Improves intestinal mucosal structure, increased villus height, and crypt proliferation[1],[2]
- **Antimicrobial effects**
  - Antibacterial, antiviral, and antiparasitic protein
  - Inhibits growth, adhesion, translocation, and virulence of pathogens[3],[4]
  - Sequesters iron
- **Immune modulation**
  - Stimulates cells involved in innate and acquired immunity[5]



1. Reznikov EA, et al. *J Nutr.* 2014;144:1401-1408. 2. Li Q, et al. *Mol Biol Rep.* 2014;41:2119-2128. 3. Ochoa TJ, *Biochimie.* 2009;91:30-34. 4. Teraguchi S, et al. *Appl Environ Microbiol.* 1995;61:4131-4134. 5. Shan T, et al. *J Anim Sci.* 2007;85:2140-2146.

Gut Permeability and Human Milk: A Specific Role of LACTOFERRIN on the Nascent Gut

Intestinal permeability changes as a function of age and type of feeding

Gut permeability and mucosal trophic effect of human milk are key factors for prevention of infections and NEC

- The feeding of human milk may modulate the trophism of the gastrointestinal tract of preterms, with more rapid maturation of intestinal epithelium (Goldman AS. *J Nutr.* 2000)
- The feeding of human milk (vs formula) is associated with decreased permeability at 28 days of age (Shulman RJ, et al. *Pediatr Res.* 1998)

Is this related to LACTOFERRIN? Probably YES, based on a number of studies:

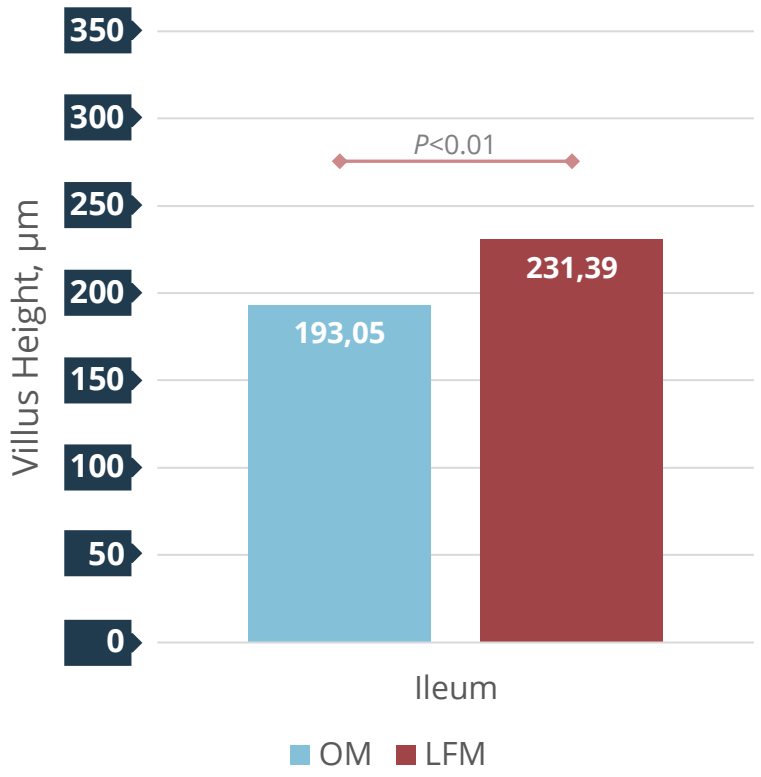
- Buccigrossi, et al. *Ped Res.* 2007 (in vitro study)
- Lonnerdal, et al. *JPGN.* 2012
- Jiang, et al. *JPGN.* 2014
- Reznikov, et al. *J Nutr.* 2014 (piglet study)

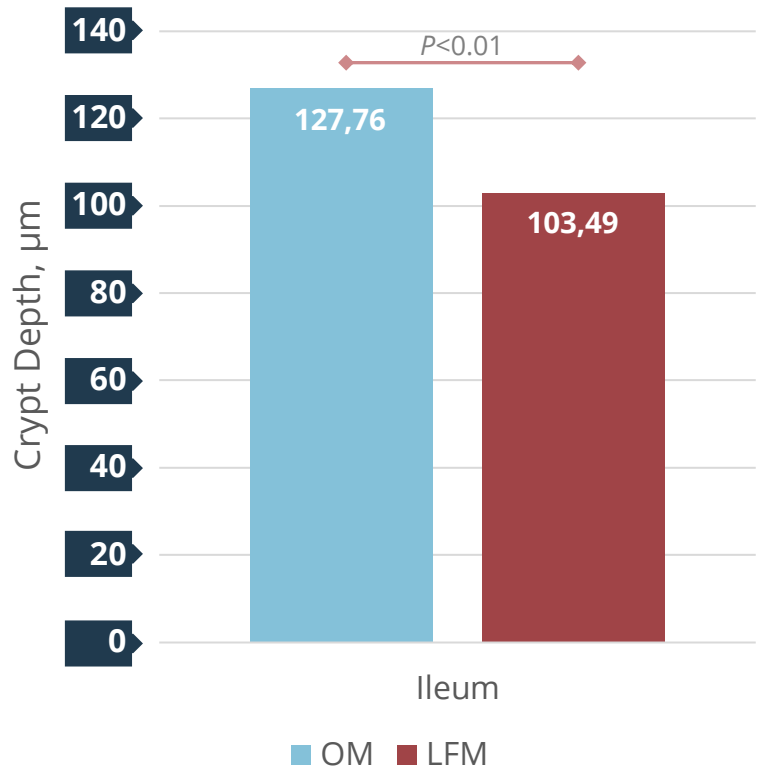
Goldman AS. *J Nutr.* 2000;130:426S-431S; Shulman RJ, et al. *Pediatr Res*. 1998;44:519-523; Buccigrossi V, et al. *Pediatr Res.* 2007;61:410-414; Lönnerdal B, et al. *J Pediatr Gastroenterol Nutr.* 2011;53:606-614; Jiang R, et al. *J Pediatr Gastroenterol Nutr.* 2014;59:642-652; Reznikov EA, et al. *J Nutr.* 2014;144:1401-8..

Lactoferrin and Intestinal Mucosa Development: Preclinical Data in Animal Model (1)

Feeding with high LF milk for 30 days **improved intestinal mucosal structure** compared to control milk, with greater villus height and reduced crypt depth in ileum.

Figure. **Newborn piglets fed cow milk with low vs high LF content**





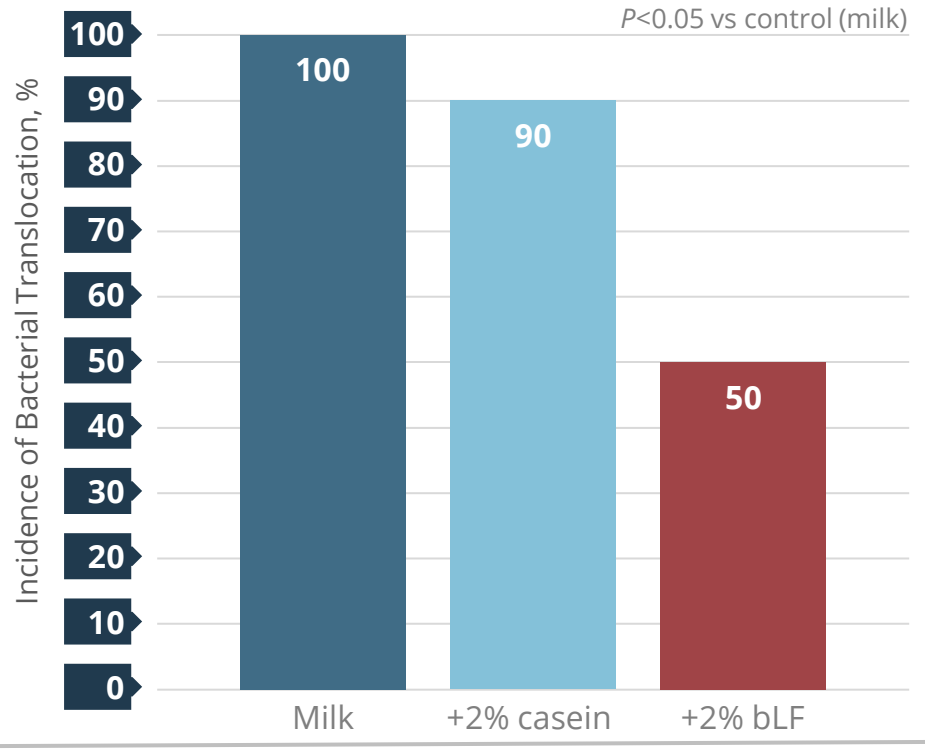
OM, ordinary cow milk; LFM, cow milk enhanced with recombinant human lactoferrin.

Li Q, et al. *Mol Biol Rep*. 2014;41:2119-2128.

Lactoferrin, Intestinal Mucosal Development and Impact On Immune Defense: Preclinical Data in Animal Model (2)

Supplementation of bovine milk for 7 days with lactoferrin significantly **decreased bacterial translocation through the mucosal epithelium.**

Figure. **Mice fed bovine milk with or without LF supplementation**



Teraguchi S, et al. *Appl Environ Microbiol*. 1995;61(11):4131-4134.

Lactoferrin and Its Trophic Effect on the Enterocytes and Gut Function in Human Infants

PEDIATRIC RESEARCH
Vol. 61, No. 4, 2007

Lactoferrin Induces Concentration-Dependent Functional Modulation of Intestinal Proliferation and Differentiation

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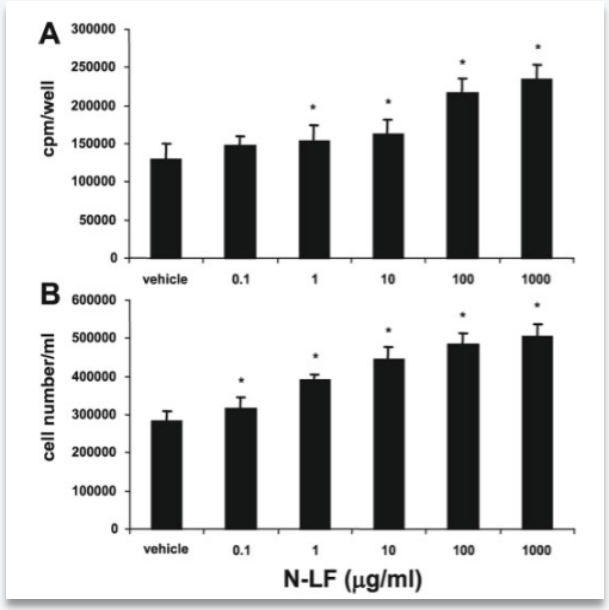
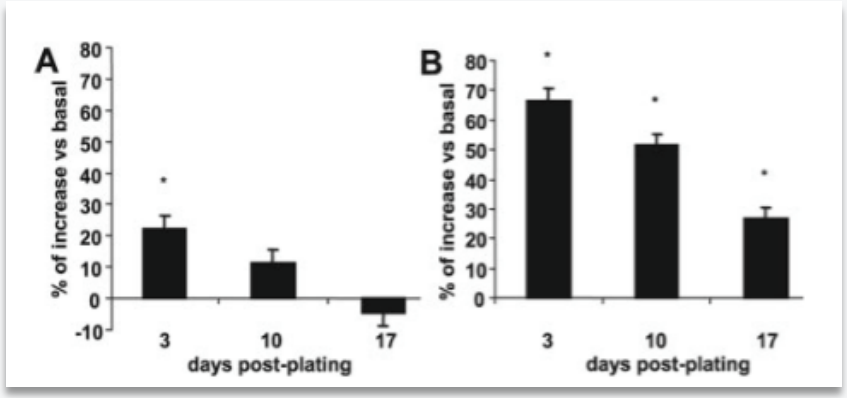
- This study assesses the in vitro effects of a wide range of bovine and human lactoferrin concentrations on:
  - Proliferation of rapidly growing enteric Caco-2 cells (as number of enterocytes)
  - Differentiation of enteric Caco-2 cells (as sucrase and lactase activities)
    - Bovine LF was compared with human LF
    - Bovine LF was used in concentrations equimolar to human LF

Buccigrossi V, et al. *Pediatr Res.* 2007 Apr;61(4):410-414.

1 – Lactoferrin has a trophic effect on the enterocytes related to its concentrations
→ the higher the LF concentrations, the faster the enterocytes proliferate





2 – Lactoferrin promotes gut function related to its concentrations
→ the lower the LF concentrations, the faster the enterocytes differentiate

These actions occurred with both bovine and human LF

Conclusions

1. Lactoferrin is a key modulator of the intestinal epithelium development. This has been shown in animal and human model studies

   Speculation → less permeability, less colonizing pathogens that can disseminate to bloodstream, less infections

2. Bovine and human lactoferrin have similar actions on the nascent gut

   → Commercial bLF is biologically active as well as purified bLF and hLF

   → Commercial bLF exerts several of the bioactivities of hLF if added to infant formula (Lönnerdal, *JPGN.* 2011; Jiang, *JPGN.* 2014)

bLF, bovine lactoferrin; hLF, human lactoferrin.

Lönnerdal B, et al. *J Pediatr Gastroenterol Nutr.* 2011 Dec;53(6):606-614;
Jiang R, et al. *J Pediatr Gastroenterol Nutr.* 2014;Nov;59(5):642-652.