Milk protein fends off sepsis in premature babies

A protein common in human milk, lactoferrin, prevents sepsis in preterm babies of very low birth weight (VLBW), who often die from this condition, according to a recent clinical report[1]. Paolo Manzoni *et al.*[1] fed such infants bovine lactoferrin or lactoferrin plus a probiotic thought to enhance its activity, *Lactobacillus rhamnosus* GG. They then measured the effects on 'late-onset' sepsis, occurring more than 72 hours after birth and before discharge. Addition of the probiotic did not give lactoferrin an edge, and lactoferrin itself did not have a statistically significant effect on the incidence of sepsis in the heavier babies (between 1,000 and 1,500 g)—perhaps because they received proportionately lower dosages than lighter babies. But, together, the findings point to a robust effect: sepsis affected 9 of 153 infants receiving either lactoferrin or lactoferrin plus the probiotic, compared to 29 out of 168 infants who received placebo.

Jeffrey Actor:

The new findings have the potential to profoundly affect the treatment of low birth weight neonates. The data dovetail with the ability of lactoferrin to promote the proper colonization of enteric bacteria, leading to maturation and growth of the intestine. Although the exact mechanism in the neonatal treatment with lactoferrin is unknown, it may operate directly through antimicrobial activity and indirectly by countering the activity of bacterially released endotoxin, thereby ameliorating inflammation and gut pathology.

A longer-term study incorporating a dose range of lactoferrin—ideally the humanized recombinant protein—will hopefully be performed in both VLBW and low-birth-weight groups. These infants have an uphill battle because of compromised development of systemic immunity. Indeed, lactoferrin has immunomodulatory functions that include accelerated reconstitution of both cellular and humoral immune responses.

Lactoferrin could give such infants a head start to accelerate their development, improve their survival rates and, in particular, prevent necrotizing enterocolitis tissue injury that may lead to incidence of sepsis.

Professor, Pathology and Laboratory Medicine, University of Texas–Houston Medical School, Houston, Texas, USA.

Victor Nizet:

The new approach is attractive for reducing the use of broad-spectrum antibiotic therapies and the attendant complications of resistant pathogens and invasive *Candida albicans* infections. Studies indicate that lactoferrin's immune defense function could derive from iron sequestration or the lytic action of its derivative peptides against microbial cell walls. Rather, I suspect a more complicated mechanism underlies the apparent protective activity: lactoferrin may shape the development and population structure of the newborn enteric flora and consequently influence the maturation of the enteric epithelial barrier and mucosal innate immune response pathways. Metagenomic approaches to analyze the intestinal microbiome in treated and untreated neonates could prove fruitful in this regard.

Professor of Pediatrics and Pharmacy, University of California San Diego, La Jolla, California, USA.

John Marshall:

Lactoferrin sequesters iron—an important microbial cofactor—and binds endotoxin—a cardinal microbial inflammatory trigger. Its presence in breast milk and its capacity to target potential pathogens in the gastrointestinal tract create a compelling biologic rationale for this study.

The conclusion that lactoferrin is beneficial is convincing, although the study is underpowered to draw any inferences about the utility of adding lactobacilli, or about differential efficacy in the lowest birth weight infants. Moreover, the apparent benefit in reducing sepsis-related mortality must be interpreted with caution, given the challenges of ascribing causality in complex diseases such as those of prematurity.

Differences in the development and patterns of colonization of the gastrointestinal tract between infants and adults make generalization of these results to an adult population difficult.

Nonetheless, nosocomial sepsis in the critically ill is frequently a consequence of alterations in gut physiology, bacteriology and barrier function, and endotoxemia—presumably of gut origin—is a very common feature of a broad spectrum of acute, life-threatening, but noninfectious, disorders such as rupture of an abdominal aortic aneurysm and necrotizing pancreatitis. Furthermore, techniques that suppress pathologic gut colonization in the critically ill such as selective decontamination of the digestive tract have shown convincing evidence of benefit in preventing nosocomial infection and improving survival. A trial evaluating lactoferrin administration as a prophylactic strategy in critically ill patients at risk of nosocomial sepsis is warranted.

Professor of Surgery, University of Toronto, Toronto, Ontario, Canada.

Victor Herson:

Among the available strategies to prevent serious late-onset infections in VLBW infants, exclusive or partial feedings with the mother's own milk is the safest and most effective. The benefit of lactoferrin in this study was similar whether infants were receiving preterm formula or human milk—which contains additional protective components including leukocytes and immunoglobulins.

The results of a similar US clinical trial recently begun will also be of great interest in confirming these impressive findings and determining the efficacy of a synthetic human alternative to bovine lactoferrin.

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1. Manzoni, P. *et al.* Lactoferrin supplementation to prevent nosocomial infections in preterm infants *J. Am. Med. Assoc.* **302**,1421–1428 (2009).

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