



LACTOFERRIN FOR INFANTS AND CHILDREN: A REVIEW OF ITS MECHANISMS OF ACTION AND THE MIXED CLINICAL EVIDENCE

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ABSTRACT

Infections remain a leading cause of illness and death in infants and young children, and the steady rise of antimicrobial resistance makes the search for safe host-directed agents more pressing. Lactoferrin, an iron-binding glycoprotein of the transferrin family, is abundant in human colostrum and is now produced at scale from bovine milk and by recombinant routes. This narrative review brings together experimental and clinical work on its use in pediatric infectious and inflammatory disease. We first outline its structure, natural sources and iron forms. We then describe how it acts against bacteria, viruses and fungi: by withholding iron, damaging microbial membranes, releasing the cationic peptide lactoferricin, degrading virulence factors and blocking biofilm formation. Its immunomodulatory side is discussed next, including neutralization of lipopolysaccharide, dampening of NF- κ B-driven cytokine release, support of phagocyte and dendritic-cell function, and regulatory T-cell responses. A third section covers its effects on the immature gut, namely epithelial growth and maturation, barrier tightening and the promotion of bifidobacteria. The clinical record is then examined. Early trials in very-low-birth-weight neonates, led by an 11-center Italian trial, reported large falls in late-onset sepsis and necrotizing enterocolitis, but two large multicenter trials, ELFIN and LIFT, found no significant benefit. Newer small trials and pooled analyses still point to a low-certainty fall in late-onset sepsis. Trials in older infants and children suggest modest effects on the severity of diarrheal and respiratory illness. We close by discussing product quality, dosing, safety and the trial designs needed to settle where lactoferrin truly helps sick children.

Keywords: Lactoferrin; Lactoferricin; Neonatal sepsis; Necrotizing enterocolitis; Immunomodulation; Gut microbiota; Pediatric infection.

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1. INTRODUCTION

Children carry a heavy share of the global burden of infection. In 2019 roughly five million children died before their fifth birthday, and infections such as pneumonia, diarrhea and neonatal sepsis were among the leading causes [1]. Preterm and low-birth-weight neonates are the most exposed group. Their skin and gut barriers are thin, their innate immune cells respond poorly, and they spend weeks in units where invasive devices and broad-spectrum antibiotics are routine [2,3]. At the same time resistant germs are spreading. In 2019, 1.27 million deaths were directly caused by bacterial antibiotic resistance [4]. These factors have

led clinicians to explore for preventive and adjunctive therapies that assist the host rather than attack the microorganism alone. The obvious model is human milk. Breastfed newborns experience fewer and less severe illnesses, and much of this protection is due to bioactive milk proteins [5]. Lactoferrin is one of those, one of the most prevalent. It is an 80 kDa iron-binding glycoprotein first discovered in milk in the mid-20th century and subsequently identified in tears, saliva, airway fluid and in the secondary granules of neutrophils [6,7]. Over the last three decades it has been demonstrated to kill or slow bacteria, prevent viruses entering the cell, modulate immune cells and help the maturation of the young intestine [8,9]. Bovine lactoferrin is currently available in tonnes and recombinant human variants have entered therapeutic trials [10,11]. These qualities make lactoferrin an interesting choice in paediatrics but the clinical tale has become more difficult. Small studies were promising before large neutral trials [12,13]. Thus, this narrative review attempts to link mechanistic results to the clinical record. It discusses the composition and

sources of lactoferrin, its antibacterial, immunomodulatory and gastrointestinal effects, the trials in neonates and older children and the practical difficulties of dose, safety and quality of product that may explain the inconsistent findings.

1.1. Review design and literature search

This article is a narrative review. It does not follow a systematic-review protocol, and no new pooled analysis was performed. The literature was searched in PubMed/MEDLINE, Scopus, Web of Science and Google Scholar from 1977 to January 2025. Search terms combined “lactoferrin”, “lactoferricin” or “talactoferrin” with “neonate”, “preterm”, “infant”, “child”, “sepsis”, “necrotizing enterocolitis”, “diarrhea”, “respiratory infection”, “immunomodulation”, “microbiota” and “intestinal barrier”. Experimental studies, randomized and non-randomized clinical trials, systematic reviews and meta-analyses relevant to infants and children were considered. Reference lists of key trials and reviews were also screened. Studies were selected by two authors on the basis of relevance and design, and randomized trials and meta-analyses were given priority when they were available. Only articles published in English were included; conference abstracts, editorials and non-peer-reviewed reports were excluded.

2. STRUCTURE, SOURCES AND FORMS OF LACTOFERRIN

Lactoferrin is a single polypeptide chain of about 690 amino acids folded into two similar halves, the N-lobe and the C-lobe, joined by a short α -helical hinge [14]. Each lobe holds one ferric ion together with a carbonate anion in a deep cleft. Binding is very tight. Lactoferrin keeps its iron down to about pH 3, far below the point at which serum transferrin releases it, so it can still hold iron in inflamed tissue or in the acidic stomach [6,14]. This protein is highly basic, with an isoelectric point of between 8 and 9. Most of this positive charge is included in the N-terminal part, which is also the site of the antimicrobial peptide lactoferricin [15,16]. Lactoferrin from humans and cows have about a 70% sequence identity. They differ in glycosylation and in certain fine aspects of iron release but most functions are preserved [10,17]. Generally two types of iron are described. Apo-lactoferrin contains no or very little iron, but holo-lactoferrin is saturated. Native milk lactoferrin is primarily in the apo or low saturation state and this form is the stronger iron chelator [17]. Commercial products have a wide range of iron saturation and processing by heat treatment can unfold the protein and inhibit some actions [10,17]. These details are clinically important. The two experiments, both claiming to employ “bovine lactoferrin”, may in reality be utilising rather distinct molecules (Figure 01).

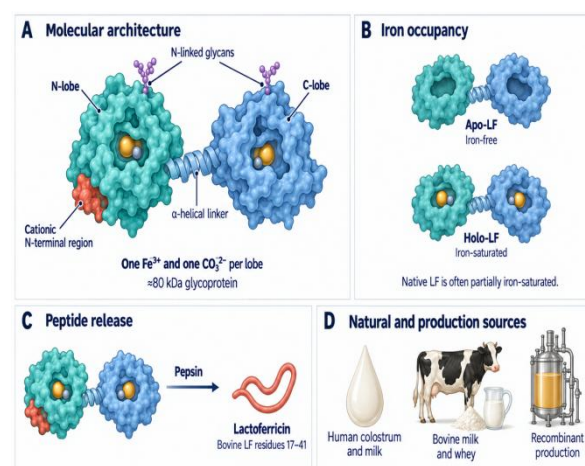


Figure 01: Illustrated structure of lactoferrin, its iron forms and its main sources. Each lobe binds one Fe^{3+} ion with a carbonate anion; the cationic N-terminal region gives rise to lactoferricin after peptic digestion.

Drawn from data in refs. [6,14,17].

Human milk is the richest natural source. Colostrum carries the highest levels, often several grams per litre, and concentrations fall over the first weeks as milk matures [18]. Maternal diet, stage of lactation, prematurity and geography all add variation [19]. Mature cow's milk contains much less, which is why bovine lactoferrin is extracted from large whey streams by cation-exchange chromatography [10]. Recombinant human lactoferrin has been expressed in rice, fungi and other systems; one such product, talactoferrin, has been tested in preterm infants [11,20]. The main features of the human and bovine proteins are compared in Table 1.

Lactoferrin is also part of the body's own response to infection, not only a food protein. Neutrophils store it in their secondary granules and release it at sites of inflammation, so its level rises in plasma, airway fluid and stool during infection [7,21]. Its glycan chains are not decoration either. They protect the protein from proteolysis and help it reach the intestine in an active form [6,17]. Seen this way, oral lactoferrin is less a drug than an attempt to restore a defense that preterm and formula-fed infants receive only in small amounts.

Table 01: Main features of human and bovine lactoferrin relevant to pediatric use.

Feature	Human lactoferrin	Bovine lactoferrin	Refs.
Molecular mass	~80 kDa glycoprotein	~80 kDa glycoprotein	[6,17]
Structure	Two lobes (N and C), one Fe^{3+} site each	Same bilobal fold; ~70% sequence identity with human	[10,14]

Feature	Human lactoferrin	Bovine lactoferrin	Refs.
Iron retention	Holds iron to about pH 3	Similar acid stability	[14]
Main natural source	Colostrum and breast milk	Cow's milk and whey	[10,18]
Lactoferricin	From the N-terminal region (residues 1-47)	Lactoferricin B (residues 17-41)	[15,16]
Uptake in infant gut	Intestinal lactoferrin receptor	Also bound and taken up by the human receptor	[22]
Regulatory status	Recombinant forms in trials	Approved as a food ingredient, including infant formula	[11,23]

3. ANTIMICROBIAL ACTIVITY

3.1. Iron withholding and direct membrane effects

The oldest known action of lactoferrin is simple. It takes iron away. Most bacterial pathogens need iron to grow, and apo-lactoferrin binds free iron so tightly that bacteria are left short of it. This bacteriostatic effect was the first to be described and it still explains part of the protection seen in milk [6,24]. It is not the whole story, however. In 1977 Arnold and colleagues showed that human lactoferrin killed bacteria outright, an effect that could not be blocked simply by adding iron [25]. Later work explained why. The cationic surface of lactoferrin binds lipopolysaccharide on Gram-negative bacteria and pulls it out of the outer membrane. The membrane becomes leaky, and the cell is also exposed to lysozyme and other milk factors [26]. In Gram-positive organisms a comparable interaction occurs with lipoteichoic acid [24,27]. Membrane damage and iron withholding seem to work together. A bacterium whose outer membrane has been loosened becomes more sensitive to antibiotics, to lysozyme and to the complement system, which may explain why lactoferrin often looks stronger in milk or serum than in clean buffer [9,24].

3.2. Lactoferricin and other derived peptides

When lactoferrin meets pepsin in the stomach, it is cut into smaller fragments. The best known of these is lactoferricin. Bellamy and co-workers identified it as the bactericidal domain of the protein and found that

the bovine peptide, covering residues 17 to 41, was more potent than the intact molecule [15]. Lactoferricin is rich in arginine and tryptophan. It forms an amphipathic loop that inserts into microbial membranes, and it also acts on intracellular targets [16,27]. This matters for infants, whose gastric acid output is lower than in adults. Partial digestion in the infant stomach may therefore release active peptides while leaving a good share of intact protein to reach the intestine [8,17]. Other fragments, including lactoferrampin and small N-terminal peptides, have also shown activity, and they may act in concert with the parent protein [27]. The relative weight of each fragment in vivo is still not known.

3.3. Anti-virulence and anti-biofilm actions

Several studies show that lactoferrin can disarm bacteria without killing them. It has a weak serine-protease activity. With this activity it cleaves the Hap adhesin and the IgA1 protease of *Haemophilus influenzae* [28]. In *Shigella flexneri* it degrades the Ipa invasion proteins, and in enteropathogenic *Escherichia coli* it breaks down EspA and EspB, which are key parts of the type III secretion system [29,30]. Both pathogens are major causes of diarrhea in young children, so these effects have direct relevance [31]. Lactoferrin also blocks biofilm growth. Singh and colleagues showed that, at levels below those that inhibit growth, it kept *Pseudomonas aeruginosa* moving across surfaces by twitching motility, so the cells never settled into mature biofilms [32]. Biofilms on catheters and endotracheal tubes are a common source of late-onset neonatal sepsis, which gives this finding practical weight [2].

3.4. Antiviral and antifungal effects

The antiviral action of lactoferrin works mostly at the early stage of infection. It binds heparan sulfate and other cell-surface glycosaminoglycans that many viruses use as first contact points, and in some cases it binds the virus particle itself [33]. Activity has been reported against rotavirus, respiratory syncytial virus, adenovirus, enteroviruses and noroviruses, all frequent pathogens in children [33,34]. Against fungi, lactoferrin and its peptides disturb the cell membrane of *Candida* species and work in synergy with fluconazole and other antifungal drugs [35]. Recombinant human lactoferrin was also synergistic with vancomycin, gentamicin and antifungals against coagulase-negative staphylococci and *Candida albicans* isolated from septic neonates [36]. The main mechanisms are summarized in Figure 2 and Table 2. Invasive candidiasis is rare in older children but carries high mortality in extremely preterm infants, so an agent that is both antifungal and safe to feed has obvious appeal [2,37].

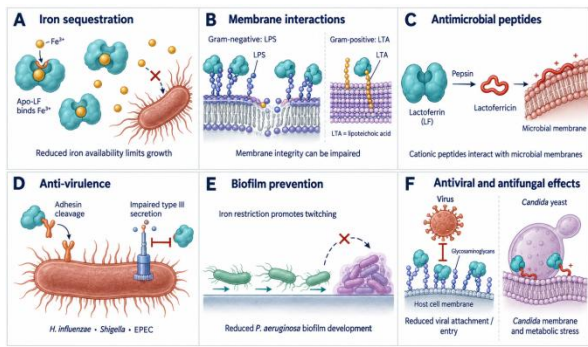


Figure 02: Illustration of the six main antimicrobial mechanisms of lactoferrin discussed in Section 3. Based on refs. [15,25,26,28,32,33,35].

Table 02: Selected experimental studies on the antimicrobial actions of lactoferrin against pathogens relevant to children.

Pathogen	Lactoferrin form	Main finding	Ref.
Gram-negative enteric bacteria	Human / bovine LF	Release of LPS and outer-membrane damage	[26]
<i>Streptococcus mutans</i> and others	Human LF (apo form)	Direct bactericidal effect, not reversed by iron	[25]
Broad panel of bacteria	Bovine lactoferricin (17-41)	Stronger killing than the intact protein	[15]
<i>Haemophilus influenzae</i>	Human milk LF	Cleavage of Hap adhesin and IgA1 protease	[28]
<i>Shigella flexneri</i>	Human LF	Degradation of Ipa invasion proteins; less invasion	[29]
Enteropathogenic <i>E. coli</i>	Human / bovine LF	Loss of EspA/EspB; type III secretion impaired	[30]
<i>Pseudomonas aeruginosa</i>	Human LF	Biofilm prevented through increased twitching motility	[32]

Pathogen	Lactoferrin form	Main finding	Ref.
Coagulase-negative staphylococci, <i>Candida albicans</i>	Recombinant human LF	Synergy with antibiotics and antifungals used in neonatal units	[36]
Rotavirus, RSV, adenovirus and others	Bovine / human LF	Block of viral attachment and entry	[33,34]

4. IMMUNOMODULATORY ROLES

4.1. Innate immunity and control of inflammation

Lactoferrin is not only a weapon. It is also a messenger that helps the immune system decide how strongly to respond [38,39]. A key link is lipopolysaccharide (LPS). By binding LPS, lactoferrin keeps it away from the CD14 and Toll-like receptor 4 (TLR4) complex on monocytes. In monocytic cells exposed to LPS, lactoferrin lowered the release of tumor necrosis factor- α , interleukin (IL)-6 and IL-8, and this effect ran through the NF- κ B pathway [40]. The picture is not purely suppressive. Ando and colleagues found that human lactoferrin can itself switch on NF- κ B through TLR4, while blocking the much stronger signal from LPS [41]. In other words, it seems to set a moderate level of alertness rather than shutting the system down. Reviews describe this as a two-way effect: lactoferrin raises defense when the host is unprepared and restrains it when inflammation becomes harmful [21,42].

Neonatal immune cells may profit from both sides of this balance. In macrophages derived from cord-blood monocytes, human lactoferrin reduced pro-inflammatory cytokine release after bacterial challenge [43]. In other models it improved phagocytosis and intracellular killing, raised natural killer cell activity and promoted maturation of dendritic cells and other antigen-presenting cells [44,45]. Iron is also part of the story. Free iron drives the formation of hydroxyl radicals in inflamed tissue. By holding iron, lactoferrin limits this oxidative damage and also helps to correct the iron disturbance that accompanies inflammation [46].

Context seems to determine which impact wins. In a host with a weak innate defence, lactoferrin tends to activate neutrophils and macrophages. It tends to moderate the reaction in a host that is already inundated with LPS or cytokines [21,42]. This is exactly the conundrum of the septic preterm newborn who may have both inadequate bacterial clearance and a harmful cytokine storm. The similar rationale may explain the preventive role of lactoferrin in animal models of endotoxemia and colitis, but only limited activity in healthy humans [47,48]. For a protein that

buffers immune responses in both directions, it is difficult to find a single biomarker and clinical testing is complicated.

4.2. Adaptive immunity in early life

Lactoferrin also regulates adaptive responses. Animal study suggests it can drive an imbalanced response back toward the middle, enhancing Th1 activity where it is weak and preventing excessive Th2 responses in allergy models [49]. This is crucial as the newborn immune system is naturally orientated toward Th2. In a randomised trial of 50 preterm newborns, oral bovine lactoferrin (200 mg/day) was associated with fewer culture-proven nosocomial sepsis episodes (4.4 vs 17.3 per 1000 patient-days; $p = 0.007$). Regulatory T-cell levels did not differ between groups at birth or at discharge, but individual increases were larger with lactoferrin [50]. If confirmed, such a rise in regulatory T cells may help the infant tolerate food antigens and commensal bacteria while still reacting to pathogens. These pathways are drawn together in Figure 3. It should be said, though, that most of this evidence comes from cell and animal models, and the doses used there do not always match what an infant receives by mouth [21,45]. Even so, the clinical observation that breastfed infants handle infections better than formula-fed ones fits well with these findings. Human milk delivers lactoferrin together with secretory IgA, lysozyme, oligosaccharides and live cells, and these factors probably act as a team [5,38]. Lactoferrin alone is unlikely to copy the whole effect, and expectations for single-protein supplements should be set with this in mind [39].

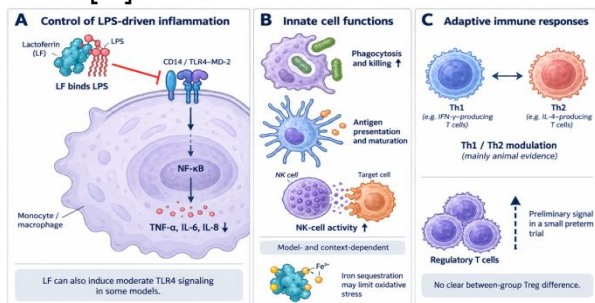


Figure 03: Illustration of the immunomodulatory actions of lactoferrin on innate and adaptive immunity. Arrows show increase (↑) or decrease (↓). Based on refs. [40,41,43,44,49,50].

5. GUT HEALTH-PROMOTING ROLES

5.1. Epithelial growth, maturation and barrier function

The gut of a preterm infant is immature. Its villi are short, its tight junctions are loose and its digestive enzymes are low. Lactoferrin is one of the milk signals that drive this tissue forward. Part of the ingested protein survives digestion and binds a specific lactoferrin receptor on enterocytes, and bovine lactoferrin is also recognized and taken up by the human receptor [22]. Inside the cell it activates signaling pathways tied to growth [51]. In Caco-2 intestinal cells the effect depended on concentration. Higher concentrations, in the $\mu\text{g/mL}$ range with a peak

at 100 $\mu\text{g/mL}$, stimulated proliferation. Lower concentrations, in the ng/mL range, raised differentiation markers such as sucrase and lactase activity [52]. Lactoferrin also protects the barrier. In epithelial models it prevented the loss of tight-junction proteins and the rise in permeability caused by inflammatory cytokines and invasive bacteria [53]. A leaky barrier allows bacteria and toxins to cross into the blood, a step thought to be central in necrotizing enterocolitis [3]. Receptor expression and lactoferrin uptake are high during early life, which suggests the infant gut is built to read this signal [51]. Formula-fed and preterm infants, who receive little or no human lactoferrin, may therefore miss part of the normal growth cue at the very time it is most needed [5,8].

5.2. Shaping the infant microbiota

Early colonization of the gut has lasting effects on immune development. Lactoferrin appears to favor beneficial bacteria. *Bifidobacterium* and *Lactobacillus* species need little iron and some can even use lactoferrin-bound iron, whereas many Proteobacteria are inhibited when iron is scarce [54]. In mother-infant pairs, higher lactoferrin levels in breast milk were linked to higher counts of bifidobacteria and lactobacilli both in milk and in infant feces [55]. Not every study agrees, and some strains of bifidobacteria are themselves slowed by lactoferrin in vitro [54]. Still, the overall trend fits the idea that lactoferrin helps to build a protective, bifidobacteria-rich community (Figure 4). This link is clinically relevant. Gut dysbiosis, with a bloom of Proteobacteria and a shortage of bifidobacteria, often comes before NEC and late-onset sepsis in preterm infants [3,9]. Clinical trials have rarely measured the microbiota. The largest such study is MAGPIE, a mechanistic cohort nested within the ELFIN trial. It enrolled 479 infants in 13 UK hospitals and analysed 1304 stool samples from 201 infants by 16S rRNA gene sequencing [72]. Lactoferrin explained less than 1% of the variation in microbiome composition, whereas hospital site explained 16% and postnatal age 6%. Shannon diversity at 34 weeks' corrected age did not differ between groups (1.24 vs 1.06; $p = 0.11$) [72]. So, at trial doses and in units with high human-milk use, the bifidogenic effect seen in laboratory and observational work was not reproduced. Whether other doses, products or lower-resource settings give a different result remains one of the clearest gaps in the field.

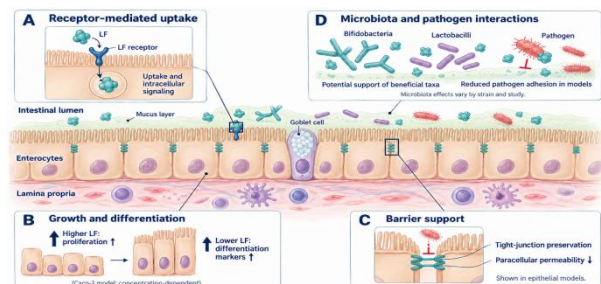


Figure 04: Illustration of the gut health-promoting effects of lactoferrin in the infant intestine: receptor-mediated signaling, barrier support, enrichment of

bifidobacteria and lactobacilli, and reduced pathogen adhesion. Based on refs. [22,52–55].

5.3. Inflammatory bowel conditions in children

Lactoferrin has a second place in pediatric gastroenterology, as a marker. Neutrophils release it into the gut when the mucosa is inflamed, and fecal lactoferrin is now used as a non-invasive marker of intestinal inflammation in children with inflammatory bowel disease [56]. As a treatment, the data are mostly from animals. In rat colitis, oral lactoferrin reduced mucosal injury and corrected the balance between pro- and anti-inflammatory cytokines [48]. Whey-protein products containing lactoferrin have also been tried as add-on therapy for *Helicobacter pylori*, with some gain in eradication rates, though most of these data come from adults [57]. Pediatric trials in these conditions are still lacking.

6. CLINICAL EVIDENCE IN PAEDIATRIC DISEASE

6.1. Neonatal sepsis and necrotizing enterocolitis

Neonatal sepsis and necrotizing enterocolitis (NEC) are the two conditions where lactoferrin has been studied most. The first strong signal came from Italy. In a multicenter trial in 11 tertiary neonatal units, Manzoni and colleagues randomized 472 very-low-birth-weight infants to bovine lactoferrin 100 mg/day, lactoferrin plus *Lactobacillus rhamnosus* GG, or placebo. Culture-proven late-onset sepsis fell from 17.3% (29/168) in the placebo group to 5.9% (9/153) with lactoferrin (RR 0.34, 95% CI 0.17–0.70) and 4.6% (7/151) with the combination (RR 0.27, 95% CI 0.12–0.60) [12]. A secondary analysis of the same trial showed fewer invasive fungal infections [37]. In an extended cohort of 743 infants from 13 Italian and New Zealand units, NEC (stage ≥ 2) fell from 5.4% to 2.0% with lactoferrin alone (RR 0.37, 95% CI 0.14–1.01; $p = 0.055$) and to 0% with the probiotic combination [58]. Smaller trials from Turkey, India and Peru pointed the same way, although not all reached statistical significance [50,59,60]. Early systematic reviews were therefore optimistic [61,62].

The picture changed with two large pragmatic trials. ELFIN, run in 37 UK hospitals, randomized 2203 infants born before 32 weeks to bovine lactoferrin 150 mg/kg/day (maximum 300 mg/day) or sucrose placebo until 34 weeks' postmenstrual age. Its primary outcome was broader than in the Italian trial. It counted late-onset infection that was either microbiologically confirmed or clinically suspected. This outcome occurred in 316/1093 infants (29%) given lactoferrin and 334/1089 (31%) given placebo (adjusted RR 0.95, 95% CI 0.86–1.04; $p = 0.23$), so the difference was not statistically significant [13]. Microbiologically confirmed infection alone did not differ either (190/1093 vs 180/1089; RR 1.05, 99% CI 0.87–1.26) [13]. LIFT, run in 16 Australian and New Zealand units, gave bovine lactoferrin 200 mg/kg/day to infants under 1500 g and compared them with infants given no supplement. Death or major morbidity occurred in 162/770 (21%)

and 170/771 (22%), respectively (RR 0.95, 95% CI 0.79–1.14) [63]. A recombinant human product, talactoferrin, was safe in a smaller trial but did not settle the question of efficacy [11]. The contrast between the Italian trial and ELFIN is shown in Figure 5. Because the two trials used different outcome definitions, the rates in the figure should not be compared directly.

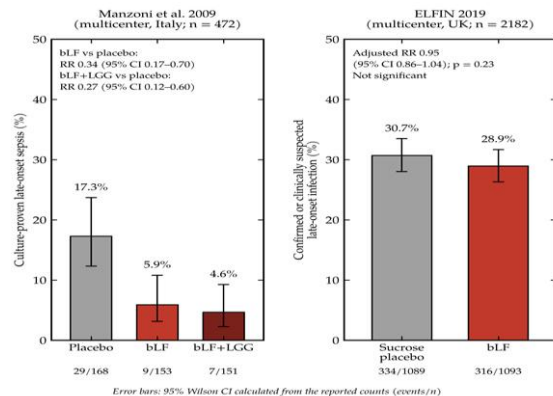


Figure 05: Late-onset infection in two landmark multicenter randomized trials of bovine lactoferrin (bLF) in preterm infants: Manzoni et al. 2009 (multicenter, Italy; 11 units) and ELFIN 2019 (multicenter, UK; 37 hospitals). The outcomes differ.

Manzoni et al. counted culture-proven late-onset sepsis, whereas ELFIN counted late-onset infection that was microbiologically confirmed or clinically suspected.

Bars show the reported proportions, with events/n below each bar (ELFIN: 2203 randomized, 2182 analysed for the primary outcome). Error bars are 95% Wilson confidence intervals calculated from the reported counts; the relative risks are those reported in the original publications [12,13]. The ELFIN difference was not statistically significant. LGG, *Lactobacillus rhamnosus* GG.

Why did the results diverge? Several explanations have been offered. Baseline sepsis rates and the share of infants fed their mother's own milk differed between settings. The age at the first dose and the length of supplementation also varied between trials. The lactoferrin products also differed in source, heat history and iron saturation [13,64]. The 2020 Cochrane update, which included ELFIN, still found pooled data pointing to fewer cases of late-onset sepsis (12 trials, 5425 infants; RR 0.80, 95% CI 0.72–0.89), but rated the certainty of evidence as low and found no clear effect on NEC (RR 1.10, 95% CI 0.86–1.41) or mortality (RR 0.90, 95% CI 0.69–1.17) [65]. A separate meta-analysis reached a similarly cautious view and stressed the heterogeneity between trials [66]. The main trials are listed in Table 3. For the practicing neonatologist, the honest reading is that lactoferrin appears well tolerated but its benefit in well-resourced units with high human-milk use is uncertain. Its value may be greater in settings where sepsis rates are high and donor milk is not available, as in some low- and middle-income countries [60,64].

Trials published after the Cochrane update add some signal, mainly from small studies in high-risk settings. In a single-center Spanish trial of 103 preterm infants (≤ 1500 g and/or ≤ 32 weeks; 50 lactoferrin, 53 placebo), bovine lactoferrin 150 mg/kg/day (maximum 300 mg/day) for up to four weeks lowered culture-confirmed late-onset sepsis (adjusted RR 0.54, 95% CI 0.31–0.93; $p = 0.028$), against a high placebo rate of 39.6% [73]. The trial did not reach its planned sample of 132 because of the COVID-19 pandemic, and its immune and antioxidant outcomes were exploratory [73]. In a three-arm trial of 305 low-birth-weight infants in Pakistan, culture-proven sepsis occurred in 7.8% (8/102) with placebo, 1.0% (1/102) with 150 mg/day ($p = 0.020$) and 4.9% (5/101) with 300 mg/day ($p = 0.39$) [74]. The authors themselves concluded that lactoferrin did not prevent sepsis, and the lack of a dose–response calls for caution [74]. A 2025 meta-analysis of pediatric randomized trials found fewer infants with late-onset sepsis (OR 0.60, 95% CI 0.42–0.86) and with diarrhea (OR 0.56, 95% CI 0.41–0.75), but no clear effect on upper respiratory infection (OR 0.61, 95% CI 0.27–1.40) [75]. These newer data fit the view that any benefit is most likely where baseline sepsis rates are high. They do not overturn the null results of the two largest trials.

Table 03: Clinical trials of lactoferrin in neonates, infants and children (previous studies). All are randomized except Egashira et al. (2007).

Study (setting)	Population (N)	Intervention, dose and duration	Main outcome (numeric result, 95% CI)	Ref.
Manzoni et al., 2009 (multicenter, Italy; 11 NICUs)	472 VLBW infants (bLF 153; bLF+LGG 151; placebo 168)	bLF 100 mg/day $\pm$ LGG vs placebo; from day 3 for 4 weeks (1001–1500 g) or 6 weeks (≤ 1000 g)	Culture-proven LOS 5.9% (9/153) and 4.6% (7/151) vs 17.3% (29/168); RR 0.34 (0.17–0.70) and 0.27 (0.12–0.60)	[12]
Manzoni et al., 2012 (same trial; secondary analysis)	Same 472 VLBW infants	As above	Invasive fungal infection 0.7% (bLF) and 2.0% (bLF+LGG) vs 7.7%; $P = .002$ and $.02$; CIs not reported	[37]
Manzoni et al., 2014 (multicenter, Italy and New Zealand; 13 NICUs)	743 VLBW infants (bLF 247; bLF+LGG 238; control 258)	bLF 100 mg/day $\pm$ LGG; to day 30 (day 45 if < 1000 g)	NEC stage ≥ 2 : 2.0% (5/247) and 0% (0/238) vs 5.4% (14/258); bLF alone RR 0.37 (0.14–1.01), $p = 0.055$	[58]
Akin et al., 2014 (single center, Turkey)	50 preterm neonates (VLBW or < 32 weeks; 25 per arm)	Oral bLF 200 mg/day vs placebo, throughout the hospital stay	Culture-proven nosocomial sepsis 4.4 vs 17.3 per 1000 patient-days ($p = 0.007$); larger individual rise in Treg; per-arm counts and CIs not reported	[50]
Kaur and Gathwala, 2015 (single center, India)	130 neonates < 2000 g (bLF 63; placebo 67)	Weight-banded bLF doses vs placebo, days 1–28 of life	Culture-proven LOS 3.2% (2/63) vs 13.4% (9/67); RR 0.21 (0.04–1.02); $p = 0.036$	[59]
Ochoa et al., 2015 (3 neonatal units, Peru)	190 neonates 500–2500 g (95 per arm)	bLF 200 mg/kg/day vs maltodextrin, 4 weeks	Clinical or culture-proven LOS 12.6% (12/95) vs 22.1% (21/95); RR 0.57 (0.30–1.09); $p = 0.085$ (NS)	[60]
Sherman et al., 2016 (multicenter, USA)	Preterm infants ($n = 60$ per arm); birth weight 750–1500 g	Talactoferrin (rhLF) 150 mg/kg twice daily vs placebo from ≤ 24 h of birth through day 28 of life	Safe and well tolerated; efficacy not established; hospital-acquired infections: 10/60 (16.7%) TLF vs 20/60 (33.3%) placebo, 50% reduction ($P < 0.04$)	[11]
ELFIN, 2019 (multicenter, UK; 37 hospitals)	2203 infants < 32 weeks (bLF 1099; placebo 1104); 2182 analysed	bLF 150 mg/kg/day (max 300 mg/day) vs sucrose, to 34 weeks PMA	Confirmed or clinically suspected LOI 29% (316/1093) vs 31% (334/1089); aRR 0.95 (0.86–1.04); $p = 0.23$ (NS)	[13]
LIFT, 2020 (multicenter, Australia and New Zealand; 16 NICUs)	1542 infants < 1500 g (770 vs 771 analysed)	bLF 200 mg/kg/day vs no supplement, to 34 weeks PMA (at least 2 weeks)	Death or major morbidity 21% (162/770) vs 22% (170/771); RR 0.95 (0.79–1.14); $p = 0.60$ (NS)	[63]

Study (setting)	Population (N)	Intervention, dose and duration	Main outcome (numeric result, 95% CI)	Ref.
Plaza-Astasio et al., 2025 (single center, Spain)	103 infants ≤ 1500 g and/or ≤ 32 weeks (bLF 50; placebo 53)	bLF 150 mg/kg/day (max 300 mg/day) vs placebo, up to 4 weeks	Culture-confirmed LOS aRR 0.54 (0.31–0.93); $p = 0.028$; placebo rate 39.6%	[73]
Ariff et al., 2025 (single center, Pakistan)	305 LBW infants 1000–<2500 g (102/102/101)	bLF 150 or 300 mg/day vs placebo, 28 days	Culture-proven sepsis 1.0% (1/102; $p = 0.020$) and 4.9% (5/101; $p = 0.39$) vs 7.8% (8/102); CIs not reported	[74]
Zavaleta et al., 2007 (Peru)	140 children aged 5–33 months with acute diarrhea (3 arms)	Rice ORS with rhLF and lysozyme vs WHO-ORS or rice ORS; 14-day follow-up	Diarrhea duration 3.67 vs 5.21 days ($P = 0.05$); no difference in stool volume or new episodes	[20]
Egashira et al., 2007 (Japan; non-randomized)	234 children <5 years analysed (LF 136; control 98)	bLF about 100 mg/day (tablet or yogurt) vs no intake, 12 weeks	Rotavirus gastroenteritis 4.4% vs 5.1% ($p = 0.81$); fewer and shorter vomiting and diarrhea episodes in infected children	[67]
Ochoa et al., 2013 (Peru)	555 children aged 12–18 months (bLF 277; placebo 278)	bLF 0.5 g twice daily vs maltodextrin, 6 months	Incidence 5.43 vs 5.15 episodes/child-year (RR 1.05, 0.94–1.18); longitudinal prevalence 6.6% vs 7.0% ($p = 0.017$); episode duration ratio 0.89 (0.80–0.99)	[68]
Chen et al., 2016 (multicenter, China)	260 infants aged 4–6 months; three groups: lactoferrin-fortified formula (FG), control formula (CG) and breastfed reference (BG)	Formula with bLF 38 mg/100 g powder vs the same formula without bLF, 3 months	Lower incidence of respiratory infection and diarrhea-related illness ($P < 0.05$); FG and BG had significantly fewer episodes than CG for both outcomes	[69]
Motoki et al., 2020 (Japan)	109 children aged 12–32 months (LF 60; placebo 49); 101 analysed	Formula giving LF 48 mg/day vs placebo formula, 13 weeks	Acute GI symptoms 41.5% (22/53) vs 62.5% (30/48); risk difference 0.21 (0.02–0.40); $p = 0.046$; respiratory symptom days 9 vs 15 ($p = 0.030$)	[70]

aRR, adjusted relative risk; bLF, bovine lactoferrin; CI, confidence interval; GI, gastrointestinal; LBW, low birth weight; LF, lactoferrin; LGG, *Lactobacillus rhamnosus* GG; LOI, late-onset infection; LOS, late-onset sepsis; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NS, not significant; ORS, oral rehydration solution; PMA, postmenstrual age; rhLF, recombinant human lactoferrin; RR, relative risk; Treg, regulatory T cells; VLBW, very low birth weight. Values in parentheses after RR or OR are 95% CIs, except where stated. Bracketed items are still to be checked against the full text.

6.2. Infectious diarrhea in infants and children

Outside the neonatal unit, diarrhea is the obvious target. In Peruvian children aged 12 to 18 months, bovine lactoferrin given for six months did not lower the number of diarrhea episodes (5.43 vs 5.15 episodes per child-year; RR 1.05, 95% CI 0.94–1.18). It did, however, reduce the longitudinal prevalence of diarrhea (6.6% vs 7.0% of days; $p = 0.017$), shorten episodes (4.8 vs 5.3 days; $p = 0.046$) and lower the share of episodes with moderate or severe dehydration (1.0% vs 2.6%; $p = 0.045$) [68]. Earlier, a rice-based oral rehydration solution containing recombinant human lactoferrin and lysozyme shortened acute diarrhea in Peruvian children aged 5–33 months (3.67 vs 5.21 days; $P = 0.05$), without a significant effect on stool volume or new episodes [20]. In a non-randomized Japanese study, daily intake of lactoferrin-containing products (about 100 mg/day) did not change the incidence of rotavirus gastroenteritis (4.4% vs 5.1%), but infected children had fewer and shorter episodes of vomiting and diarrhea [67]. In a placebo-controlled trial in Japanese toddlers, a formula giving 48 mg lactoferrin/day for 13 weeks lowered the prevalence of acute gastrointestinal symptoms (41.5% vs 62.5%; $p = 0.046$) and the number of days with respiratory symptoms (median 9 vs 15; $p = 0.030$) [70]. The experimental findings on *Shigella* and enteropathogenic *E. coli* provide a plausible basis for these effects [31]. Overall, lactoferrin looks more likely to soften illness than to prevent it, at least at the doses used so far. This pattern fits the experimental work, which shows mainly anti-virulence and barrier effects rather than outright killing at the

concentrations found in the gut lumen [31,53]. It also suggests that lactoferrin might be most useful as an add-on to oral rehydration and zinc rather than as a stand-alone preventive.

6.3. Respiratory infections and other conditions

Respiratory infections have received less attention in children. In a Chinese trial, weaned infants fed an iron-fortified formula with bovine lactoferrin had fewer episodes of both diarrhea and respiratory tract infection (260 infants aged 4–6 months; 38 mg lactoferrin per 100 g of powder for 3 months; $P < 0.05$ for both) [69]. Meta-analyses that pooled adult and pediatric trials found that lactoferrin lowered the risk of respiratory tract infections (OR 0.57, 95% CI 0.44–0.74 in one analysis; OR 0.78, 95% CI 0.61–0.98 for infants and children in another) [47,71]. These pooled results include different products, doses and age groups, so they should be read with care. Pooled reviews of the main trials are summarized in Table 4. There is also interest in lactoferrin for recurrent wheeze, otitis media and viral infections in day-care children, but these uses rest mainly on laboratory work and small studies [33,34]. Until trials in these groups are done, any benefit should be regarded as possible rather than proven.

Table 04: Reviews and meta-analyses of lactoferrin supplementation relevant to children.

Review	Scope	Main conclusion (pooled estimate, 95% CI)	Ref.
Turin et al., 2014	Narrative review of 11 registered neonatal trials (>6000 infants)	Protective trend in early trials; larger trials needed; no pooled estimate	[61]
Sharma et al., 2017	Systematic review, lactoferrin in neonatal care	Promising for sepsis and NEC; evidence of limited quality; narrative synthesis of clinical trials available through 2016 (no pooled meta-analytic estimates reported)	[62]
Pammi and Suresh, 2020 (Cochrane)	12 RCTs, 5425 preterm infants, including ELFIN	LOS RR 0.80 (0.72–0.89), low certainty; NEC RR 1.10 (0.86–1.41); mortality RR 0.90 (0.69–1.17)	[65]
Razak and Hussain, 2021	10 RCTs, 3679 preterm infants	LOS RR 0.56 (0.36–0.86; $I^2 = 58\%$), low certainty; NEC RR 0.62 (0.29–1.33); mortality RR 0.74 (0.36–1.53)	[66]
Ali et al., 2021	RCTs, respiratory infections, all ages (6 pooled; $n = 1194$)	Respiratory tract infection OR 0.57 (0.44–0.74)	[71]
Berthon et al., 2022	25 studies on inflammation, immunity and RTI (20 in adults)	RTI in infants and children OR 0.78 (0.61–0.98); adults OR 1.00 (0.76–1.32)	[47]
Mayorga et al., 2025	RCTs in children <18 years (25 studies)	LOS OR 0.60 (0.42–0.86); diarrhea OR 0.56 (0.41–0.75); upper respiratory infection OR 0.61 (0.27–1.40), NS	[75]

CI, confidence interval; LOS, late-onset sepsis; NEC, necrotizing enterocolitis; NS, not significant; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; RTI, respiratory tract infection.

7. SAFETY, DOSE AND PRODUCT QUALITY

No consistent safety signal has emerged, but the data should be read with care. Lactoferrin is a normal part of human milk, and the European Food Safety Authority judged bovine lactoferrin safe as a food ingredient, including in infant formula [23]. In ELFIN, two serious adverse events, both in the lactoferrin group, were judged possibly related to the intervention: one case of blood in the stool and one death after intestinal perforation probably associated with NEC. Causality was not established [13]. In LIFT, two suspected unexpected serious adverse reactions in the lactoferrin group (unexplained late jaundice and inspissated milk syndrome) were not attributed to the intervention, and one fatal case of inspissated milk syndrome occurred in the control group [63]. Smaller

trials reported no serious adverse events attributable to lactoferrin [12,60,73]. Dose is harder to fix. Neonatal trials used fixed doses of 100 mg/day or weight-based doses of 150–200 mg/kg/day [12,13,60,63]. Studies in older children used up to 1 g/day [68]. A pooled analysis of human-milk studies gave mean lactoferrin levels of 4.91 g/L in milk from the first 28 days and 2.10 g/L in mature milk [18]. For an infant on full enteral feeds of about 150 mL/kg/day (an illustrative volume), this equals roughly 740 mg/kg/day from early milk and 315 mg/kg/day from mature milk. Trial doses of 100 mg/day, or 150–200 mg/kg/day (capped at 300 mg/day in ELFIN), are therefore well below early-milk intake but close to the intake from mature milk [12,13,63]. In the first days of life, however, feed volumes are small, and preterm milk has

been little studied [18]. Real intake thus depends on feed volume, milk stage and the share of maternal milk. Some trial doses may still have been too low, especially for infants who received little maternal milk [64]. Product quality is perhaps the most overlooked factor. Pasteurization and spray-drying can denature lactoferrin and change its iron saturation, and these changes may weaken its antimicrobial and receptor-binding activity [10,17]. Few trials reported the iron saturation, purity or heat history of the product they used. One practical caution also applies. Bovine lactoferrin is a cow's milk protein. Highly purified products contain few other milk allergens, but their use in infants with proven cow's milk protein allergy has not been well studied and calls for care. Iron load is not a concern at the doses used, since the amount of iron carried even by holo-lactoferrin is small compared with dietary intake [23].

8. GAPS AND FUTURE DIRECTIONS

There are several gaps. First, the laboratory-to-bedside gap is large. Many mechanistic experiments employed concentrations or methods not achievable by oral feeding. Second, trial populations need to be defined more clearly. The greatest benefit may be in settings where baseline infection rates are high, where human milk is a limited supply, or in the most immature newborns, although trials to far have not been powered to evaluate such subgroups [64,65]. Third, there must be standards for products. Future trials should report the source, purity, iron saturations and processing of the lactoferrin utilised and ideally prove its activity prior to use [17]. Fourth, combinations are worth exploring. Italian trials suggested a possible interaction between lactoferrin and probiotics. Laboratory work has shown synergy with antibiotics and antifungals [12,36]. Finally, children outside newborn units have been researched insufficiently. To see if lactoferrin deserves a position alongside current preventive efforts, well-designed trials in diarrhoea, respiratory infection and paediatric inflammatory bowel disease, particularly in poor and middle income countries, may be in order [1,4]. Core outcome sets would be helpful also. The definition of sepsis (culture-proven only in the Italian trial; confirmed or clinically suspected in ELFIN), NEC staging, and reporting of fungal infection were different between trials and this made pooling more difficult than it should have been [65,66]. New formulations is another open area. Recombinant human lactoferrin circumvents the problem of cow's milk and yields a specific product, while encapsulation and peptide-based versions may protect action across the stomach [11, 17]. Manufacturers have also been enhancing bovine products by learning how to minimise heat damage during purification [10]. These versions have not yet been compared head-to-head in babies.

9. CONCLUSION

Lactoferrin is one of the most multifunctional proteins in human milk. It binds iron, destroys microbial membranes, releases lactoferricin and disarms virulence factors. It also reduces detrimental inflammation, encourages immunological maturation and enables the newborn gut to develop, seal its barrier and host good microorganisms. The biology is plausible. The clinical evidence is weaker. Small early trials in preterm infants revealed considerable decreases in sepsis and NEC but the two largest trials did not confirm a benefit and pooled assessments now evaluate the evidence as low in certainty. More recent modest trials in high-risk settings continue to report fewer culture-proven infections. Data in older children imply lesser diarrhoeal and respiratory disease, rather than true protection. Part of the discrepancy may be due to variances in goods, doses and settings rather than a lack of effect. The next stage isn't more of the same. Better defined products, sensible dosing, targeted high risk populations, and trials that measure both clinical and mechanistic outcomes. With these in place, lactoferrin has potential to be a powerful host-directed tool in paediatric infection.

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12. AUTHOR CONTRIBUTION

Both are contributed equally.

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