



DOSSIER · SUBSTANCE

Lactoferrin

Lactoferrin is a milk glycoprotein that is widely studied in research. This page classifies the human studies: It shows which application areas have been tested in controlled trials and why the most frequently cited works in the field do not consistently concern lactoferrin itself.

467

STUDIES IN
TOTAL

191

IN HUMANS

116

OF WHICH
CONTROLLED

38

IN ANIMALS

35

IN THE LAB

Figures from the IHR study database · Last updated 2026-10-15

How to Read This Dossier

ESTABLISHED

measured in humans, with a
comparison group

PLAUSIBLE

supported by mechanism, animal
studies or observation

HYPOTHESIS

a likely connection that still needs to
be tested

Lactoferrin at a Glance

ORIGIN:

Lactoferrin is an iron-binding glycoprotein that occurs in milk and colostrum. In research it appears as bovine lactoferrin obtained from cow's milk, as a protein derived from human milk and as recombinantly produced human lactoferrin. Part of the literature examines it not alone, but in mixtures with lysozyme, probiotics or other milk proteins such as osteopontin.

EVIDENCE BASE:

467 evaluated papers · 116 controlled human studies · 75 observational studies · 61 review articles · 38 animal studies · 28 cell-culture studies

STRONGEST EVIDENCE:

- Immune system: In a randomised, placebo-controlled double-blind study in healthy formula-fed infants, the 26 lactoferrin-fed infants experienced significantly fewer lower-respiratory-tract illnesses (0.15 vs. 0.5 episodes/year; $P < 0.05$) than the 26 infants receiving standard formula ³.
- Gut and microbiome: In a randomised, double-blind, placebo-controlled study in 104 participants with polyps ≤ 5 mm, daily intake of 3.0 g bovine lactoferrin over 12 months significantly slowed the growth of adenomatous polyps in participants aged 63 years or younger ¹⁰.
- Gut: In an international, multicentre, randomised, double-blind, placebo-controlled study in 743 VLBW neonates, a reduction in NEC incidence was observed in the treatment groups, with the combination of bovine lactoferrin and Lactobacillus rhamnosus GG showing the strongest effect ².
- Safety and tolerability: A 2020 Cochrane review assessed enteral lactoferrin supplementation for the prevention of sepsis and NEC in preterm infants and indicated safe use, although the evidence for some endpoints was rated as uncertain ⁵.
- Gut and microbiome: In a study in children with diarrhoea, addition of recombinant human lactoferrin and lysozyme to a rice-based oral rehydration solution significantly shortened diarrhoea duration (3.67 vs. 5.21 days; $P = 0.05$) and increased the proportion of children with formed stool after 48 hours (85 % vs. 69 %; $P < 0.05$) ⁶.

LIMITATIONS:

- Most controlled human studies concern the immune system and the gut; the antiviral, metabolic, cognitive, oncological, bioavailability and bone areas are markedly smaller.
- Some studies test lactoferrin only as a component of a mixture, so no conclusion about lactoferrin as a single substance can be drawn from them.
- The most frequently cited controlled human study examines gastric digestion and not a health endpoint; the most-cited paper in the database is classified as an animal study.

CLASSIFICATION:

Lactoferrin is an iron-binding glycoprotein of milk that is investigated in controlled human studies primarily for the immune system and the gut.

1. What Lactoferrin Is

Lactoferrin is an **iron-binding glycoprotein** that occurs in milk and colostrum and appears in research in several forms: as **bovine lactoferrin** obtained from cow's milk, as a protein derived from human milk and as **recombinantly** produced human lactoferrin. The papers in the database examine it both as an isolated substance and as a component of enriched dairy products and infant formula. For the evaluation of individual studies this distinction is decisive: no conclusion about lactoferrin as a single substance can be drawn from an investigation of a mixture.

The decisive point for all studies is the passage of the substance through the body. When lactoferrin is taken **orally**, **gastric transit** determines in which form it reaches the intestine; a frequently cited 2001 paper examined precisely this digestion of bovine lactoferrin in adults. It follows that findings from cell culture and animals cannot be transferred directly to oral use in humans. Added to this is the **variety of forms**: bovine, human and recombinant lactoferrin are not identical, and some studies test lactoferrin only as a component of a mixture. Anyone reading the literature must therefore first clarify which substance in which form and by which route was examined.

2. What the Studies Show in Detail

The key human studies and the most important reviews — by application area, with population, duration, preparation, measured variable and result as reported in the original papers. Numbers appear only where the paper states them.

Distribution of **controlled human studies** by application area — the numbers are not additive, as one paper may be assigned to several areas:

APPLICATION AREA	CONTROLLED STUDIES
Immune system	61
Gut and microbiome	40
Safety and tolerability	37
Inflammatory processes	33
Viral infections	14
Metabolism	11

APPLICATION AREA	CONTROLLED STUDIES
Cognition and psyche	5
Oncology	4

Gut and Microbiome

Twelve healthy adults (age 21 ± 0.3 years) received, in a randomised crossover design on three separate days via nasogastric intubation, a test drink containing 4.5 g bovine lactoferrin (LF): either 20 % iron-saturated LF (apoLF) with gastric-pH buffer (0.1 mol/L sodium citrate/citric acid; apoLFbuf), apoLF without buffer (apoLF) or iron-saturated LF (holoLF). Gastric emptying rate did not differ between the drinks. The gastric survival rate of LF, analysed by gel-permeation chromatography under denaturing conditions, was 64 % (apoLFbuf), 62 % (apoLF) and 79 % (holoLF). Addition of the buffer lowered intragastric pH initially but did not raise it over a longer period and therefore did not inhibit intragastric LF degradation. The authors conclude that after oral administration substantial amounts of apoLF and holoLF survive gastric transit ¹.

In a randomised, placebo-controlled double-blind study in healthy formula-fed infants (≥ 34 weeks gestation, ≤ 4 weeks old) the children received either a lactoferrin-enriched formula (850 mg/L) or a commercial cow's-milk-based formula (102 mg/L) for 12 months. The 26 infants fed the lactoferrin-enriched formula experienced significantly fewer lower-respiratory-tract illnesses (0.15 episodes/year) than the 26 infants receiving standard formula (0.5 episodes/year; $P < 0.05$), mainly wheezing. In addition, significantly higher haematocrit values were observed after 9 months (37.1 % vs. 35.4 %; $P < 0.05$) in the lactoferrin-enriched-formula group. The lactoferrin-supplemented formula was well tolerated ³.

In a randomised, double-blind, placebo-controlled study of 104 participants aged 40 to 75 years with polyps ≤ 5 mm in diameter that were likely adenomas, participants received either placebo, 1.5 g bovine lactoferrin (bLF) or 3.0 g bLF daily for 12 months. Target polyps were monitored colonoscopically. Intake of 3.0 g bLF significantly slowed the growth of adenomatous polyps in participants aged 63 years or younger. The authors note that removal of adenomatous colorectal polyps is a preventive measure against bowel cancer, yet polyps may be missed and polypectomy is not always 100 % effective. The study suggests that daily intake of 3.0 g bLF could be a clinically useful adjunct to colorectal polyp removal ¹⁰.

In a double-blind, placebo-controlled, randomised clinical study of 48 adult women with recurrent bacterial vaginosis, all participants received metronidazole (500 mg twice daily) for 7 days and were simultaneously randomised to either a probiotic mixture of *Lactobacillus acidophilus* GLA-14 and *Lactobacillus rhamnosus* HN001 in combination with bovine lactoferrin or placebo (2 capsules/day for 5 days, followed by 1 capsule/day for 10 consecutive days; induction phase). Verum or placebo administration (1 capsule/day for 10 consecutive days) was repeated every month (maintenance phase) during the six-month follow-up from the first day of the menstrual cycle. Normalisation of the Nugent score, resolution of symptoms and recurrences were assessed. The results indicate a benefit of the combination, although the study was designed as a pilot study ¹².

In a prospective, placebo-controlled, double-blind, randomised study of very-low-birth-weight (VLBW) preterm infants or those born before the 32nd week of gestation, infants received either placebo ($n = 25$) or 200 mg lactoferrin ($n = 25$) daily during their hospital stay. Episodes of culture-confirmed nosocomial sepsis and necrotising enterocolitis (NEC) were recorded. FOXP3+CD4+CD25hi lymphocytes were examined by flow cytometry at birth and discharge. A third comparison group consisted of healthy term newborns ($n = 16$). Treg levels at birth and discharge were similar, while preterm infants showed significantly lower values than term controls. Individual increases in Treg levels were higher in the LF group ¹³.

In an observational study of 30 healthy adult volunteers, the influence of First Leaf (FL; consisting of blackcurrant extract powder, lactoferrin and lutein) and Cassis Anthomix 30 (CAM30; blackcurrant extract powder) on the intestinal microbiota and markers of colorectal cancer risk was examined. Fluorescence in situ hybridisation for faecal microbiota analysis showed that intake of FL and CAM30 led to significant increases ($P < 0.0001$) in populations of lactobacilli and bifidobacteria, while populations of *Clostridium* spp. and *Bacteroides* spp. decreased significantly ($P < 0.0001$). In addition, feeding of FL and CAM30 reduced β -glucuronidase activity and significantly lowered faecal pH ($P < 0.05$). The authors conclude that the results open the possibility that intake of FL and CAM30 could offer various health benefits by acting as novel prebiotic agents ⁴⁹.

Immune System

In a randomised, double-blind, placebo-controlled study of 66 volunteers without severe periodontitis, participants received either tablets containing *Lactobacillus salivarius* WB21 (6.7×10^8 CFU) and xylitol or xylitol alone (placebo) three times daily for 8 weeks. Periodontal clinical parameters and whole-saliva samples were collected at baseline, after 4 weeks and at the end of the intervention (8 weeks). Salivary lactoferrin level was measured by ELISA. Periodontal clinical parameters improved in both groups after 8 weeks. Current smokers in the test group showed significantly greater improvement in plaque index and probing depth compared with those in the placebo group. Salivary lactoferrin level was also significantly reduced in the test group of smokers. The authors conclude that probiotics may be useful for improving/maintaining oral health in high-risk individuals.

In an international, multicentre, randomised, double-blind, placebo-controlled study of 743 VLBW neonates (birth weight < 1500 g), infants were randomised to receive either bovine lactoferrin (BLF, 100 mg/day) alone (LF group; $n = 247$), BLF plus *Lactobacillus rhamnosus* GG (LGG; 6×10^9 CFU/day; BLF + LGG group; $n = 238$) or placebo (control group; $n = 258$) from birth until day 30 of life (day 45 in neonates < 1000 g). Primary endpoints were $\geq$ stage 2 NEC as well as death and/or $\geq$ stage 2 NEC before discharge. The results showed a reduction in NEC incidence in the treatment groups, with the combination with LGG having the strongest effect ².

In a randomised prospective study of 206 patients with *Helicobacter pylori* infection, patients were randomised into two groups: 101 patients (group A) received standard triple therapy (esomeprazole, clarithromycin, amoxicillin), while 105 patients (group B) received modified eradication therapy (standard triple therapy plus bovine lactoferrin and probiotics). Successful eradication was defined as a negative C13-UBT 8 weeks after completion of treatment. At the end of the study, 175/206 patients showed negative C13-UBT results. Intention-to-treat and per-protocol analyses showed an improved eradication rate in the lactoferrin and probiotics group compared with standard therapy ⁸.

Mean birth weight was 1591 ± 408 g and gestational age 32.1 ± 2.6 weeks. A total of 33 clinically defined first late-onset sepsis events occurred. Cumulative sepsis incidence in the LF group was 12/95 (12.6 %) versus 21/95 (22.1 %) in the placebo group and 20 % (8/40) versus 37.5 % (15/40) in infants ≤ 1500 g. The hazard ratio for LF after adjustment for birth weight was 0.507 (95 % CI: 0.249–1.034). There were 4 episodes of culture-confirmed sepsis in the LF

group versus 4 in the placebo group. In a secondary exploratory analysis using time since treatment start, LF reached significance. No serious adverse events attributable to the intervention occurred ¹⁴.

A 2013 analysis used data from two multicentre RCTs conducted from 2004 to 2008 in eleven tertiary neonatal intensive care units in Italy. One trial examined bovine lactoferrin supplementation for prevention of late-onset sepsis in VLBW infants. This analysis, however, examined whether exclusive feeding with fresh breast milk, compared with formula feeding, was associated with a lower risk of retinopathy of prematurity (ROP). It found an association with reduced ROP risk, not an effect attributable to lactoferrin ⁵³.

Safety and Tolerability

A 2020 Cochrane review assessed the safety and efficacy of enteral lactoferrin supplementation for prevention of sepsis and necrotising enterocolitis (NEC) in preterm infants. The authors searched CENTRAL, MEDLINE, PREMEDLINE, Embase and CINAHL up to January 2020 as well as clinical trial registers and conference reports for randomised controlled trials (RCTs) and quasi-randomised studies. Included were RCTs examining enteral lactoferrin supplementation in any dose or duration for prevention of sepsis and NEC. Secondary endpoints were duration of mechanical ventilation, development of chronic lung disease (CLD) or periventricular leukomalacia (PVL), length of hospital stay until discharge in survivors and adverse neurological outcomes at two years of age or later. The results suggest safe use, although evidence for some endpoints was rated as uncertain ⁵.

Metabolism

Absorption and excretion were monitored for 48 hours in the ORU, with continued monitoring by home and clinic follow-up for 14 days. The G-ORS and R-ORS groups showed no differences in diarrhoea outcomes and were therefore combined as the control group. Intention-to-treat analysis showed a significant shortening of diarrhoea duration (3.67 days vs. 5.21 days, $P = 0.05$) in the Lf/Lz-R-ORS group compared with the control group as well as a significant increase in the number of children achieving formed stool at 48 hours (85 % vs. 69 %; $P < 0.05$). There were no significant differences in diarrhoea volume or in the percentage of children with a new diarrhoea episode after reaching the endpoint. The authors conclude that addition of recombinant human lactoferrin and lysozyme to a rice-based oral rehydration solution had beneficial effects ⁶.

A 2021 narrative review examined milk proteins and their bioactive peptides. Milk proteins are characterised by high nutritional quality and exhibit a broad range of bioactivities, including satiety, antimicrobial, mineral-binding and antilipidaemic properties. Due to their water solubility, milk proteins can be readily separated into casein and whey fractions, which can be further fractionated into individual proteins such as alpha-S1- and alpha-S2-caseins, beta-casein, kappa-casein as well as the whey proteins alpha-lactalbumin, lactoferrin, beta-lactoglobulin and glycomacropeptide. Many of these proteins have unique bioactivities. In addition, peptides encrypted in the primary sequences of the proteins and released during digestion are increasingly recognised as biologically active protein metabolites that may have positive effects on human health. The review examines the current state of science on the contribution of milk proteins and their unique peptides and amino acids to human health ⁵².

Inflammatory Processes

In a randomised controlled study of 81 children aged six months to six years (mean age 2.31 years) hospitalised for acute diarrhoea, children received either probiotics (*Lactobacillus casei* var. *rhamnosus*; $n = 42$) or no probiotics ($n = 39$) orally twice daily for seven days. Faecal samples were collected to examine microbial content by traditional agar plate and next-generation sequencing. Immunoglobulin A (IgA), lactoferrin and calprotectin were determined by ELISA and compared between groups. Total IgA levels in faecal extracts of the probiotic group were higher than in the control group and reached statistical significance ($p < 0.05$). Concentrations of faecal lactoferrin and calprotectin, which served in this study as inflammatory markers and not as tested active substance, were significantly downregulated in patients with probiotic *Lactobacillus casei* ⁷.

In a 12-week, double-blind, placebo-controlled study of patients aged 18 to 30 years with acne vulgaris, participants were randomised to either fermented milk with 200 mg lactoferrin daily ($n = 18$, lactoferrin group) or fermented milk alone ($n = 18$, placebo group). Acne lesions and severity were assessed at monthly visits. Skin condition (hydration, sebum, pH) and skin surface lipids were evaluated at baseline and after 12 weeks. Acne improved in the lactoferrin group through significant decreases in inflammatory lesions by 38.6 %, total lesions by 23.1 % and acne severity by 20.3 % compared with the placebo group after 12 weeks. In addition, sebum content in the lactoferrin group was reduced by 31.1 % compared with the placebo group. The amount of total skin surface lipids decreased in both groups. Of the major lipids, amounts of triacylglycerols and free fatty acids decreased in the lactoferrin group, while the amount of free fatty acids decreased only in the placebo group ⁹.

Modified intention-to-treat analysis showed 28-day overall mortality of 26.9 % in the placebo group and 14.4 % in the talactoferrin group (two-sided $p = 0.052$), corresponding to an absolute reduction of 12.5 % and a relative reduction of 46.5 % ¹⁶.

A 2015 review addressed the multifunctional properties of iron-binding lactoferrin and nanomedical approaches to enhance its bioactive functions. Lactoferrin (Lf), an iron-binding protein of the transferrin family, was first isolated from milk but is also present in most exocrine secretions and in the secondary granules of neutrophils. Reports of antimicrobial and anti-inflammatory activities of lactoferrin demonstrate its importance in host defence against infections and excessive inflammation. Anticarcinogenic reports make this protein even more valuable. The review focuses on the structural configuration of iron-containing and iron-free forms of lactoferrin from various sources such as goat, camel and bovine. In addition to the specific beneficial properties of lactoferrin from each of these sources, the general antimicrobial, immunomodulatory and anticancer activities are discussed. Implementation of nanomedical strategies to enhance the bioactive function of lactoferrin is also discussed, together with information on lactoferrin in clinical trials ⁴⁶.

A 2019 pilot study examined the effect of lactoferrin on pathological sequelae of Alzheimer's disease (AD) and the influence on the p-Akt/PTEN signalling pathway. In AD patients, reduced serum levels of acetylcholine (ACh), serotonin (5-HT), antioxidant and anti-inflammatory markers as well as reduced expression of Akt in peripheral blood lymphocytes (PBL) and of PI3K and p-Akt in PBL lysate were observed; all these parameters improved significantly after daily lactoferrin administration for 3 months. Likewise, elevated serum amyloid- β (A β) 42, cholesterol, oxidative stress markers, IL-6, heat-shock protein (HSP) 90, caspase-3 and p-tau as well as elevated expression of tau, MAPK1 and PTEN in AD patients were significantly reduced after lactoferrin intake. Improvement of the mentioned AD surrogate markers after lactoferrin treatment was accompanied in this pilot study by improved cognitive function, assessed with the Mini-Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale ⁴⁷.

A 2020 review addressed lactoferrin from bovine milk as a protective companion for life. Lactoferrin (Lf), an iron-binding multifunctional glycoprotein of the transferrin family, is present in most biological secretions and reaches particularly high concentrations in colostrum and breast milk. A key function of lactoferrin is non-immune defence, and it is regarded as a mediator between innate and adaptive immune responses. Lf from bovine milk (bLf), the most important Lf used in human medicine because of its ready availability, has been classified by the US Food and Drug Administration as a food additive that is generally recognised as safe (GRAS). Among the numerous protective activities of this nutraceutical protein, the most important shown after oral administration are: antianaemic, anti-inflammatory, antimicrobial, immunomodulatory, antioxidant and anticancer activities. All these activities underline the importance of bLf in host defence, which represents an ideal nutraceutical both because of its economic production and because of its tolerability after ingestion. The review summarises the most important beneficial activities shown after oral administration of bLf and attempts to identify potential perspectives for its prophylactic and therapeutic applications in the future ⁵⁰.

Oxidative Stress

In a split-mouth randomised clinical study of 30 patients undergoing scaling and root planing (SRP), patients were randomised to two home hygiene treatments based on the following oral gels: the postbiotic-based Biorepair Parodontgel Intensive (group 1) and the chlorhexidine-based Curasept Periodontal Gel (group 2). At baseline (T0) and after 3 and 6 months (T1–T2), the following periodontal clinical parameters were recorded: probing depth (PPD), recession, tooth mobility, bleeding on probing (BoP) and plaque control record (PCR). A significant intragroup reduction was observed in both groups for PPD, BoP and PCR; conversely, recession increased significantly in both groups, while tooth mobility did not vary. Regarding intergroup comparisons, no statistically significant differences were found. Both gels, each containing antioxidant natural ingredients or chlorhexidine, are effective for home treatment of periodontitis. Further studies are required to evaluate the individual chemical compounds of the gels that are supposed to be responsible for the observed positive effect ¹¹.

Further Investigations

In a randomised clinical trial involving 48 women with recurrent vulvovaginal candidiasis (VVC) who tested positive for *C. albicans*, exhibited symptoms of VVC and had a documented history of recurrence, the women were randomised into two groups receiving either verum or placebo (2 capsules/day for 5 days, followed by 1 capsule/day for a further 10 days) as adjuvant treatment to topical clotrimazole (induction phase), followed by a 6-month maintenance cycle (1 capsule/day verum or placebo for 10 consecutive days each month). The verum formulation contained *Lactobacillus acidophilus* GLA-14, *Lactobacillus rhamnosus* HN001 and bovine lactoferrin. Symptoms, overall cure rate and recurrence rate were assessed. After clotrimazole therapy, both groups showed significant improvement in symptoms. However, only women treated with probiotics and lactoferrin showed significant improvement in itching and discharge after 3 and 6 months. During the six-month follow-up, recurrences were significantly less frequent in the intervention group than in the placebo group (33.3 % vs. 91.7 % after 3 months and 29.2 % vs. 100 % after 6 months). The authors conclude that the lactobacillus mixture studied in combination with lactoferrin represents an effective adjuvant treatment ¹⁵.

Bones and Joints

In secondary analyses of a randomised controlled trial in rural Malawi, milk samples from 659 mother-infant pairs were analysed 6 months after birth for general categories of human milk oligosaccharides (HMOs: total HMOs, fucosylated HMOs and sialylated HMOs), 51 individual HMOs and 6 bioactive proteins (lactalbumin, lactoferrin, lysozyme, antitrypsin, IgA and osteopontin). The authors examined associations of the relative frequencies of HMOs and concentrations of bioactive proteins with infant growth from 6 to 12 months (change in length-for-age Z-score, weight-for-age Z-score, weight-for-length Z-score and head circumference Z-score) as well as the ability to stand or walk alone at 12 months, and motor and language skills, socio-emotional development, executive function and working memory at 18 months. The analyses were adjusted for covariates and multiple testing. Across all participants there were inverse associations of IgA and lactoferrin concentrations with motor skills ($P = 0.018$ and $P = 0.04$ respectively) ¹⁷.

Viral Infections

A review from 2009 examined the effect of lactoferrin on enteric pathogens. Lactoferrin, an iron-binding protein with multiple physiological functions (antimicrobial, anti-inflammatory and immunomodulatory), is one of the most important proteins in mammalian milk. Protection against gastroenteritis is the biologically most probable activity of lactoferrin. Numerous in-vitro and animal studies have demonstrated a protective effect of lactoferrin against infections with enteric microorganisms, including rotavirus, *Giardia*, *Shigella*, *Salmonella* and diarrhoeagenic *Escherichia coli*. Lactoferrin has two main effects on enteric pathogens: it inhibits growth and impairs the function of surface-expressed virulence factors, thereby reducing their ability to adhere to or invade mammalian cells. Thus lactoferrin could protect infants from gastrointestinal infections by preventing the attachment of enteropathogens in the intestine. Recently several clinical studies in children have begun to investigate this question. Whether lactoferrin can prevent a significant proportion of diarrhoeal diseases remains open ⁴⁴.

A review from 2020 discussed lactoferrin as a protective natural barrier of the respiratory and intestinal mucosa against coronavirus infection and inflammation. May 2020, caused by a novel coronavirus (2019-nCoV) characterised by a spherical morphology and identified by next-generation sequencing. Although the respiratory tract is the primary entry route of SARS-CoV-2, gastrointestinal involvement with nausea, vomiting and diarrhoea can also occur. No drug and no vaccine had been approved, as there is no evidence from rigorous clinical studies. Increasing interest has been shown in the possible preventive role and adjuvant treatment of lactoferrin, a glycoprotein of human secretions that is part of a non-specific defence system and is known to play a crucial role against microbial and viral infections, exerts anti-inflammatory effects on various mucosal surfaces and can regulate iron metabolism. In this review, after analysing the properties of lactoferrin, the conception of a clinical study is proposed to evaluate and verify its effect using a dual combination treatment with a local, solubilised intranasal spray formulation and oral administration. Lactoferrin could counteract coronavirus infection and inflammation by acting either as a natural barrier of both the respiratory and intestinal mucosa or by reversing the iron disturbances associated with viral colonisation ⁴⁵.

A review from 2015 examined clinical applications of bioactive milk components. Milk represents a unique resource for translational medicine: it contains a rich pool of biologically active molecules with proven clinical benefits. The ongoing characterisation of the mechanistic processes by which milk components promote development and immunity has uncovered numerous milk-derived compounds with potential applications as clinical therapies in infectious and inflammatory diseases, cancer and other conditions. Lactoferrin is a potent antimicrobial and antiviral agent in high-risk patient populations and a potentially effective adjuvant in the chemotherapy of lung cancer. While active preclinical investigations of human milk will soon lead to large-scale

production of human milk molecules, bovine milk components in many cases represent a practical source of bioactive milk compounds for use in clinical studies. This review summarises current efforts to translate compounds from human and bovine milk into effective clinical therapies. These efforts point to a common pathway for the translation of milk-derived compounds into clinical applications ⁴⁸.

A review from 2022 examined lactoferrin as a glycoprotein that plays an active role in human health. Lactoferrin (Lf), which occurs widely in human and mammalian milk, is a multifunctional glycoprotein with many functions such as immunoregulation, anti-inflammation, antibacterial, antiviral and antioxidant activity. These extensive functions are largely due to its ability to chelate iron and interfere with cellular receptors of pathogenic microorganisms and their hosts. In addition, it is non-toxic and well compatible with other dietary supplements. Thus Lf is widely used in food nutrition, as a drug carrier, in biotechnology and in feed development. Although Lf is continuously researched and investigated, a more comprehensive and systematic compendium is still required. This review presents recent advances in the structure and physicochemical properties of Lf as well as clinical studies on human diseases, with the aim of providing a reference for further exploration of Lf and the development of related functional products ²⁶.

A review from 2024 examined the nutraceutical and health-promoting potential of lactoferrin, an iron-binding protein in humans and animals. Lactoferrin is a natural cationic iron-binding glycoprotein of the transferrin family found in bovine milk and other exocrine secretions, including tears, saliva and bile. Lactoferrin has been investigated for its numerous potent influences, including anticancer, anti-inflammatory, antioxidant, anti-osteoporotic, antifungal, antibacterial, antiviral, immunomodulatory, hepatoprotective and other health-promoting effects. Lactoferrin has shown several nutraceutical and pharmaceutical potentials and has a significant influence on improving the health of humans and animals. Lactoferrin plays a critical role in maintaining normal physiological homeostasis in relation to the development of pathological disorders. The current review highlights the medical value, nutraceutical role, therapeutic application and outstanding beneficial health properties of lactoferrin, which would benefit from further exploration of this glycoprotein for the development of effective drugs, medicines and pharmaceuticals to address various health problems in animals and humans ⁵⁴.

Skin

A mini-review from 2013 examined lactoferrin as a bioinspired anti-biofilm therapy. Medically relevant biofilms have gained significant interest, partly due to the epidemic increase in obesity and the ageing population in the developed world. The associated comorbidities of chronic wounds such as pressure ulcers, venous leg ulcers and diabetic foot wounds remain refractory to currently available therapies. The development of chronicity in the wound is primarily due to the inability to complete the wound-healing process, which is attributable to the presence of bioburden, specifically bacterial biofilms. New therapies that specifically target biofilms are clearly needed. Lactoferrin is a multifaceted molecule of the innate immune system found primarily in milk. While further investigations are required to elucidate the mechanisms of action, in-vitro analyses of lactoferrin and its derivatives have shown that these complex molecules are structurally and functionally well suited to address the heterogeneity of bacterial biofilms. In addition, the use of lactoferrin and its derivatives in the clinic has proven promising ⁵¹.

Overall Picture

Across all areas, lactoferrin emerges as an orally available glycoprotein with measurable effects in very different populations: from preterm infants through children with diarrhoea to adults with acne, sepsis or periodontitis. The range of investigated endpoints extends from clinical scores (Nugent score, acne severity, MMSE) through microbiological parameters (faecal microbiota, β -glucuronidase) to biochemical markers (haematocrit, Treg levels, p-Akt/PTEN). Dosages vary widely: 100 mg/day to 3.0 g/day in adults, 200 mg/kg/day in neonates, 850 mg/L in infant formula. The studies mostly last from 4 weeks to 12 months. Several randomised controlled trials show significant improvements, yet the effects are often limited to subgroups (e.g. smokers, participants $\leq$ 63 years) or reach only borderline significance ($p = 0.052$).

The evidence is relatively consistent for some areas such as sepsis prevention in preterm infants and diarrhoea treatment in children, while for other areas such as Alzheimer's, periodontitis or skin only individual small studies or pilot investigations are available. Transferability to clinical practice is limited, as many studies use different preparations (apoLF, holoLF, talactoferrin, enriched formula) and combinations with probiotics or other substances, so the specific effect of lactoferrin alone often cannot be isolated. In addition, long-term data on safety and efficacy beyond the follow-up periods of the studies are lacking. Open questions concern the optimal dose, the significance of iron loading and transferability to broader patient groups.

Methodology of the Evidence Base

The present works include randomised controlled trials (RCTs), placebo-controlled double-blind studies, crossover designs, observational studies and reviews. Typical intervention durations range from 4 weeks to 12 months, with follow-ups up to 6 months. Endpoints are diverse: clinical parameters (sepsis episodes, NEC, diarrhoea duration, acne lesions, periodontal indices), microbiological and immunological markers (Treg levels, IgA, calprotectin, faecal microbiota), biochemical values (haematocrit, p-Akt/PTEN, amyloid- β) and safety data. Systematically lacking are studies examining lactoferrin as monotherapy against placebo without co-interventions, as well as dose-response studies and investigations into long-term safety. Many studies are small ($n < 100$) and limited to specific populations, which restricts generalisability. In addition, different lactoferrin preparations (bovine, recombinant human, iron-saturated, apo) are used, which complicates comparison.

The Most-Cited Works Often Do Not Concern Lactoferrin

The citation peak of the field only partly concerns lactoferrin. Among the most-cited controlled works are studies on **PROBIOTICS** with *Lactobacillus salivarius* in periodontitis and on *Lactobacillus casei* in childhood diarrhoea, in whose titles lactoferrin does not appear. Another highly cited work examines the administration of **colostrum** in extremely preterm infants. Such works are linked to the lactoferrin literature via shared keywords, yet examine a different substance or mixture. Anyone who reads the citation numbers as proof of effect for lactoferrin overestimates the evidence.

For the assessment this yields a simple rule: a work counts only for the statement it itself investigated. Studies on probiotic strains, on colostrum or on enriched infant formula can support lactoferrin when they include it as a tested component, and they cannot support it when they mention it only in passing. The database makes this mixing visible because it records the type of each investigation. The next step would be to separate the works by tested substance and count the pure lactoferrin literature separately.

3. How Robust the Research Is

The research is broadly distributed. Of the controlled human studies, the largest groups fall under the **immune system** and the **intestine**, followed by investigations into **safety** and **inflammation**. Clearly smaller are the areas **antiviral**, **metabolism**, **cognition**, **oncology**, **bioavailability** and **bone**. A second focus lies on **preterm infants**: several of the most-cited works examine lactoferrin for the prevention of sepsis and necrotising enterocolitis in very small preterm infants as well as in bottle-fed infants. Alongside stand works on diarrhoea in children, on oral and gum health and on skin. The observational human works supplement this picture with associations that do not prove causation.

Methodologically the field is divided in two. On one side stand controlled studies with placebo groups, partly randomised and double-blind, which permit robust statements about tested effects. On the other side stands a large number of **basic research works**, **mechanism reviews**, **animal** and **cell-culture studies** that describe associations and pathways of action but do not prove application in humans. These preclinical findings must not be read as clinical effect. It is also striking that citation numbers do not follow study type: the most-cited work in the database is classified as an **animal study**, while the most frequently cited controlled human study examines digestion in the stomach and not a health endpoint.

4. What Is Frequently Claimed — and What the Data Provide

STATEMENT	EVIDENCE BASE
Necrotising enterocolitis and sepsis in preterm infants	Several controlled studies are available here, some randomised and placebo-controlled. They represent the best-investigated field of application, yet they predict
Periodontitis and Oral Health	The most cited periodontal study examines a probiotic preparation, not Lactoferrin. Further studies test gels with multiple components, so the effect of the indiv
Antiviral Applications	The area comprises a smaller group of controlled studies. The database permits no statement regarding individual viruses; the studies must be examined separ
Skin and Acne	A much-cited study examines fermented milk enriched with lactoferrin. Since a food and not an isolated substance was tested, it provides no statement on lacto

5. Profile: Molecule and Charge

Lactoferrin is not a single molecule, but a **mixture** — there is no molecular formula and no fixed molecular mass. What can be described are functional groups, charge behaviour and redox properties; that is precisely what the next section addresses.

6. Charge, Electrons, Radicals

Lactoferrin carries a strongly basic N-terminus, via which it binds to negatively charged surfaces of microorganisms, viruses and mammalian cells ²⁵. Iron binding is stoichiometrically determined: each molecule binds two ferri ions, in a controlled study in humans ²³. Chelation of iron and influence on cellular receptors account for a large part of the functions ²⁶; iron chelation is associated with antimicrobial, anti-inflammatory and antioxidant properties ²⁹. Iron saturation controls the orientation: apo-LF chelates iron and disrupts membrane integrity ³¹. A cation exchange in the narrower sense is not described.

On the redox side, one study names reactive oxygen formation, oxidative stress and regulation of the gut-lung axis as points to be examined ²⁴. Reviews describe that Lf lowers ROS production and mitigates oxidative tissue damage ²⁷, scavenges reactive oxygen species ²⁸ and limits free radicals ³⁰. These statements come from reviews, not from measurements in humans. Preclinically, a hydrogel showed inhibition rates of 88.6 ± 2.3 % against *Escherichia coli* and 92.7 ± 0.7 % against *Staphylococcus aureus* in cell culture ³²; in cell assays, hLF obtained from tomatoes lowered intracellular ROS accumulation ³³. What would need to be clarified is which charge and redox parameters were measured directly in humans.

7. Interactions with Other Substances

With which other substances of the platform this substance has been **jointly** investigated or discussed in human studies and reviews — combination, comparison or shared mechanism of action. The number names works in which both occur.

SUBSTANCE	SHARED WORKS	OF WHICH CONTROLLED IN HUMANS
Chronic Inflammation	124	38
Iron	72	16
Gut Microbiome	44	17
Probiotics	42	23
Stress, Cortisol and Inflammation	25	3
Art Therapy	20	4
High-Intensity Interval Training (HIIT)	15	10
Cognitive Behavioural Therapy for Insomnia (CBT-I)	8	4
Vitamin D	5	1
Zinc	4	1

Mainly combinations are described in which lactoferrin was added to an existing treatment. In a controlled study of 218 hospitalised adults with moderate to severe COVID-19, participants received 800 mg per day of oral bovine lactoferrin or placebo, each together with standard therapy against COVID-19 ³⁷. In *Helicobacter pylori*, addition of lactoferrin to standard triple therapy improved eradication rates, independent of the antibiotic used; adverse events were mild and comparable between groups ⁴⁰. In another study, probiotics and the combination of probiotics and lactoferrin improved treatment adherence, but not eradication, within sequential therapy ³⁵. In recurrent bacterial vaginosis, a probiotic mixture of *Lactobacillus acidophilus* GLA-14 and *Lactobacillus rhamnosus* HN001 together with bovine lactoferrin was investigated as an adjuvant to metronidazole ¹².

In several works lactoferrin appears in combination with further substances without the effect of the single substance having been tested. A *Lactobacilli* mixture with lactoferrin reduced recurrences markedly versus placebo (33.3 % vs. 91.7 % after 3 months and 29.2 % vs. 100 % after 6 months) ¹⁵, and vaginal detection of *L. acidophilus* and *L. rhamnosus* increased on individual days ³⁴. In very-low-birth-weight preterm infants, bovine lactoferrin alone or with LGG lowered the incidence of NEC from stage 2 as well as death and/or NEC from stage 2; no adverse effects or intolerances occurred ². In anaemia under chemotherapy, oral lactoferrin was compared with intravenous iron, each together with rHuEPO ¹⁹. Further combinations include probiotics with Pentasa in chronic inflammatory bowel diseases ³⁶, a retinoid complex with a prebiotic food supplement in acne ³⁸ as well as lactoferrin, lysozyme, *Lactobacillus*, resveratrol, vitamins and trace elements in post-COVID-19 ^{39 39}. What would need to be examined is which uptake, enzyme or binding pathways explain these combinations and whether the effects can be attributed to lactoferrin.

8. Overdosage, Tolerability, Limits

In very small preterm infants, no adverse effects or intolerances occurred under bovine lactoferrin alone or in combination with LGG in a controlled study ². A lactoferrin-enriched infant formula was well tolerated ³. In a review of randomised studies on lactoferrin for the prevention of sepsis and necrotising enterocolitis in preterm infants, none of the included works reported confirmed adverse effects from the supplemented lactoferrin ²⁰; the authors described effect and safety as controversial ²⁰. For oropharyngeal administration of colostrum in very small preterm infants, safety is regarded as confirmed ⁴².

In adults with severe sepsis talactoferrin was well tolerated in a phase-2 study; the safety profile resembled that of placebo ¹⁶. Treatment-related adverse and serious events did not differ between the groups ⁴¹. Oral administration in the same study was not associated with lower 28-day mortality and might even be harmful ⁴¹. In an eradication therapy against *H. pylori* more patients in group A than in group B reported side effects ($P < 0.05$) ⁸; in another study the incidence of side effects was 9.5 %, 9 % and 8.2 % ($P = 0.1$) ⁴³. The evidence does not state a numerical upper limit; whether dose specifications allow derivation of such a limit remains to be clarified.

9. The Most Robust Studies

Ordered by strength of evidence, not by prominence. The complete evaluation comprises considerably more studies; the most robust ones are presented here.

Controlled Studies in Humans

- ¹ Gastric digestion of bovine lactoferrin in vivo in adults (2001)
- Improvement of periodontal condition by probiotics with *Lactobacillus salivarius* WB21: a randomized, double-blind, placebo-controlled study (2008)
- ² Bovine lactoferrin supplementation for prevention of necrotizing enterocolitis in very-low-birth-weight neonates: a randomized clinical trial (2014)
- ³ A double-blind, placebo-controlled, pilot study of bovine lactoferrin supplementation in bottle-fed infants (2007)

- ⁴ Benefits of Lactoferrin, Osteopontin and Milk Fat Globule Membranes for Infants (2017)
- ⁵ Enteral lactoferrin supplementation for prevention of sepsis and necrotizing enterocolitis in preterm infants (2020)
- ⁶ Efficacy of rice-based oral rehydration solution containing recombinant human lactoferrin and lysozyme in Peruvian children with acute diarrhea (2007)
- ⁷ Probiotic *Lactobacillus casei*: Effective for Managing Childhood Diarrhea by Altering Gut Microbiota and Attenuating Fecal Inflammatory Markers (2019)
- ⁸ *Helicobacter pylori* eradication: a randomized prospective study of triple therapy versus triple therapy plus lactoferrin and probiotics (2007)
- ⁹ Dietary effect of lactoferrin-enriched fermented milk on skin surface lipid and clinical improvement of acne vulgaris (2010)
- ¹⁰ Effect of orally administered bovine lactoferrin on the growth of adenomatous colorectal polyps in a randomized, placebo-controlled clinical trial (2009)
- ¹¹ Home Oral Care of Periodontal Patients Using Antimicrobial Gel with Postbiotics, Lactoferrin, and Aloe Barbadensis Leaf Juice Powder vs. Conventional ... (2022)
- ¹² Evidence-based mixture containing *Lactobacillus* strains and lactoferrin to prevent recurrent bacterial vaginosis: a double blind, placebo controlled ... (2019)
- ¹³ Oral lactoferrin to prevent nosocomial sepsis and necrotizing enterocolitis of premature neonates and effect on T-regulatory cells (2014)
- ¹⁴ Randomized controlled trial of lactoferrin for prevention of sepsis in peruvian neonates less than 2500 g (2015)
- ¹⁵ Randomised clinical trial in women with Recurrent Vulvovaginal Candidiasis: Efficacy of probiotics and lactoferrin as maintenance treatment (2019)
- ¹⁶ A phase 2 randomized, double-blind, placebo-controlled study of the safety and efficacy of talactoferrin in patients with severe sepsis (2013)
- ¹⁷ Associations of human milk oligosaccharides and bioactive proteins with infant growth and development among Malawian mother-infant dyads (2021)
- Administration of a Multi-Strain Probiotic Product to Women in the Perinatal Period Differentially Affects the Breast Milk Cytokine Profile and May ... (2016)
- ¹⁸ Recombinant human lactoferrin ingestion attenuates indomethacin-induced enteropathy in vivo in healthy volunteers (2003)
- ¹⁹ Efficacy and safety of oral lactoferrin supplementation in combination with rHuEPO-beta for the treatment of anemia in advanced cancer patients ... (2010)
- ²⁰ Prophylactic lactoferrin for preventing late-onset sepsis and necrotizing enterocolitis in preterm infants: A PRISMA-compliant systematic review and ... (2018)
- ²¹ Use of bovine lactoferrin for *Helicobacter pylori* eradication (2003)
- ²² Evaluation of the clinical efficacy of a mouthwash and oral gel containing the antimicrobial proteins lactoperoxidase, lysozyme and lactoferrin in ... (2008)

10. Summary

In humans, controlled studies have primarily examined applications in the immune system and gut, followed by safety and inflammation. The studies show effects in preterm infants for the prevention of sepsis and necrotising enterocolitis, in formula-fed infants for the reduction of respiratory diseases, in adults with adenomatous polyps for slowing polyp growth, and in children with diarrhoea for shortening the duration. These findings come from controlled human studies, some randomised, placebo-controlled and double-blind. Digestion in the stomach has been investigated for oral use: A frequently cited study from 2001 showed that substantial amounts of bovine lactoferrin survive gastric passage. Preclinical findings from cell culture and animals describe relationships and mechanisms of action, but do not prove application in humans.

It is plausible that lactoferrin acts via iron-binding and antimicrobial properties and that the diversity of forms – bovine, human and recombinant lactoferrin – as well as the path through the body influence the results. It could follow from this that oral application in humans shows different effects than cell or animal studies. **Hypothesis:** The observed effects on gut microbiota and immune parameters could be mediated via a modulation of the intestinal flora and iron availability. Research is at an early stage; open questions concern the transferability of the findings to different populations and the significance of the dosage form.

A study would need to clarify how the different forms of lactoferrin – bovine, human and recombinant – differ in their effects in humans and what influence gastric passage has on efficacy with oral administration. It is also open whether the effects observed in combination with probiotics or lysozyme are attributable to lactoferrin alone. For the areas where the study situation is smaller – antiviral, metabolism, cognition, oncology, bioavailability and bone – controlled studies in humans would be required to examine whether the preclinical indications can be confirmed.

11. What Remains Open

- **Gastric passage:** In what form does orally ingested lactoferrin reach the intestine, and how do bovine, human and recombinant forms differ in this respect?
- **Single substance or mixture:** Which controlled studies examine lactoferrin alone, without probiotics, lysozyme or other milk proteins?
- **Transferability:** Can the findings in preterm infants be transferred to adults, and which study would decide this question?

12. Further Paths

Topics, mechanisms of action and chains in which this substance occurs — for all those who want to look beyond the substance.

- Interaction network

Frequently Asked Questions

How is the overall state of human studies to be classified?

Numerous controlled human studies exist, predominantly on the immune system, the gut, safety and inflammation. In addition there is a large number of basic, animal and cell-based studies. Only the controlled human studies count for a tested effect; the preclinical findings describe mechanisms of action and relationships, not the application. The decisive factor is always which substance was tested in which form.

Why are so many frequently cited works not lactoferrin studies?

Because the database links works via shared keywords. Studies on probiotic strains, on colostrum or on fortified infant formula then appear in the lactoferrin literature, although they test a different substance or a mixture. The citation count says nothing about whether lactoferrin itself was the tested component.

What distinguishes bovine from human lactoferrin in the studies?

Bovine lactoferrin comes from cow's milk and is the form most frequently tested in studies. Human lactoferrin occurs in human milk and is sometimes produced recombinantly. The forms are not identical, and gastric passage can alter them differently. A study on one form therefore cannot be transferred directly to another.

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Research, put in context. Every statement leads to the original paper; the decision in the individual case rests with the treating professional.
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