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Lactoferrin and its role in neonatology: a review article

Abstract

Lactoferrin (LF) is a glycoprotein, which is present in milk of mammals. It has been proven to plays a very important role in innate immune host defences. It is well known that Neonatal sepsis and necrotizing enterocolitis (NEC) are responsible for significant morbidity and mortality in the new-born, especially in VLBW (1500 grams at birth) infants. The ill effects of sepsis and NEC persist in spite of appropriate and effective antibiotic therapy and have been associated with poor long term outcome. In the few recent trials which have been conducted around the globe, in field of neonatology, role of LF in prevention of neonatal sepsis and NEC has been strengthened. Furthermore many trials are underway and only future may provide a definite answer of LF role in sepsis and NEC. This review article has been written to through some light on the recent work that has already been done, to strengthen the role of LF in neonatal sepsis and the work that is still under process.

Keywords: lactoferrin, neonatology, antimicrobial, bovine

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Abbreviations: LF, lactoferrin; NEC, necrotizing enterocolitis; VLBW, very low birth weight; HBV, hepatitis B virus; EV71, enterovirus 71; HPV, human papillomavirus; LPS, lipopolysaccharide; BLF, bovine lactoferrin; HLF, human lactoferrin; LOS, late-onset sepsis; LGG, *lactobacillus rhamnosus* groups; BPD, bronchopulmonary dysplasia; VAP, ventilator associated pneumonia; NEC, necrotizing enterocolitis; UTI, urinary tract infection

Introduction

Lactoferrin (LF) is predominately available in mammalian milk and in other secretions of body like tears and vaginal secretions.

Discovery and naming

It is an iron-binding glycoprotein and is present in human plasma in relatively low concentrations, but relative high levels are observed in colostrum, human breast milk, and seminal plasma.[1,2] Markedly higher levels occur in cord blood, tears, and vaginal mucus. "Lactoferrin" (LF) name is derived from its past classification as a major iron-binding protein in milk. LF, also referred sometimes as lacto-transferrin, was first identified in 1939 in bovine milk[2] and it was set apart from human milk in 1960.

Cutting edge research and implications (Table 1)

LF has been shown to have various functions, including antimicrobial like antibacterial, antifungal, antiviral; anti-carcinogenic; antioxidant; and immunomodulatory effects. LF is digested by the enzymes of stomach, predominantly by pepsin and the resultant secondary product of digestion is known as lactoferricin (LFcin). LFcin has more potent antimicrobial activity than parent molecule. However both these molecules are proved to have significant antimicrobial activity and thereby inhibit the growth of pathogenic bacteria, fungi, and viruses. LF is made primarily from the neutrophils but other cells also contribute to its levels in milk. The complete amino acid sequences of human LF contain 703-amino acid residues.[3-6] After few initial preclinical trials that showed positive results with LF, the first clinical trial was conducted under the guidance of Manzoni et al.[7] in Italy. Furthermore several studies are being done round the globe to measure the same hypothesis.

The investigators have reported significant reduction in incidence of death and sepsis in LF treated group. However additional large studies are needed to support the safety and efficacy of LF. In a recent review article by Berlutti et al.[8] the *Hepatitis B virus* (HBV), *Human parainfluenza virus*, *Alphavirus*, *Hantavirus*, *Human papillomavirus* (HPV), feline calicivirus, adenovirus, Enterovirus 71 (EV71), Echovirus 6, influenza A virus and Japanese encephalitis virus were added to the spectrum of LF. Trials that have been completed demonstrate a definitive role of LF in prevention of neonatal sepsis and its related mortality. Bigger try-outs are still awaited to support these findings. Before LF becomes a part of routine care, there are several significant questions that need to be asked? Is LF safe in premature/IUGR infants? What is the appropriate dose and duration? When and whom to start? What is the spectrum of antimicrobial activity? Can there be emergence of resistance? Most tests have focused on effect of LF on very low birth weight new-born babies; therefore its beneficial effect cannot be generalized. An important heated topic of argument, for use of LF in very low birth and extremely low birth weight neonates is the danger of untoward effects like allergy. LF is derived from Bovine milk and the protein can be potentially allergic to the neonates. But till now in all well conducted trials no adverse effects have been reported. Furthermore, many children who received Bovine LF in the past, as a part of clinical trials, also reported no side effects.[9,10] However long term follow up of these enrolled neonates and children's needs to be viewed to answer this question.

Mechanism of action

The proposed mechanism of action of LF is its ability to bind to iron. This theory came from the structural analysis of LF, which showed that its cationic N-Terminus harbours microbicidal activity and its structure is similar to that of the iron-binding region seen in other bactericidal molecule. The proposed mechanism of action of LF at the bacterial level is primarily by its ability to change bacterial cell wall permeability and secondary release of lipopolysaccharide (LPS) from gram-negative bacteria. LPS makes these bacteria susceptible to phagocytosis by cells of immune system. There are various other mechanisms purposed for its action.[11-15] (Table 2).

Table 1 Table showing studies which are going around the world for lactoferrin evaluation in various aspects of neonatology CRP, C-reactive protein; GOS, Galacto-Oligosaccharides; LF, Lactoferrin; LOS, Late-Onset-Sepsis; NEC, Necrotizing Enterocolitis; NICU, Neonatal Intensive Care Unit; VLBW, Very Low Birth Weight

Serial no	Study	Population	Intervention group	Control group	Outcome
1	Enteral Lactoferrin In Neonates (ELFIN); ISRCTN88261002	Neonates with gestational age less than 32 weeks in the first 72 h of age (n = 2,200)	BovineLF150mg/kg/day (maximum:300mg)until discharge	Milk with placebo	**Primary outcome** 1. Culture-proven or clinically suspected LOS from trial entry until discharge. **Secondary outcome** 1. All-cause mortality prior to hospital discharge 2. NEC: Bell's stage II or III 3. Severe retinopathy of prematurity treated medically or surgically 4. Bronchopulmonary dysplasia 5. A composite of invasive infection, major morbidity and mortality. 6. Total number of days of administration of antibiotics per infant from 72 h until death or discharge from hospital 7. Total number of days of administration of antifungal agents per infant 8. Total length of stay until discharge home 9. A range of health economic outcomes
2	Oral lactoferrin supplementation for prevention of sepsis in preterm neonate; NCT01821989	Neonates with birth weight between 500 and 2,500 g and less than 36 weeks of gestational age and admitted to the NICU in the first 48 h of age (n = 180)	Two arms: LF 100 mg/kg daily OR LF 150 mg/kg twice daily. Unspecified duration	Placebo in form of distill water	**Primary outcome** 1. Evaluate the effectiveness of oral LF in preventing culture-proven neonatal sepsis **Secondary outcome** 1. Complete blood count with differential leucocytic count. 2. Compare two dose regimen of LF Supplementation 3. Study effect of LF supplementation on serum iron stones
3	Trial of lactoferrin for prevention of infections in very premature babies (LACUNA); ISRCTN66482337	Neonates with a gestational age of 23 to 30.6 weeks admitted to the NICU in the first 48 h of age (n = 79)	Bovine LF 100 mg/day, 2 doses per day until 36 weeks gestational age or discharge	Milk without LF	**Primary outcome** 1. Death or at least one Health-care associated infections before discharge home. 2. Tolerance of LF **Secondary outcome** 1. Infections per 1,000 patient day 2. NEC 3. Surgical intervention for NEC 4. Death ascribe to acute effects of sepsis
4	Lactoferrin Infant Feeding Trial (LIFT) to prevent sepsis and death in preterm infants; ACTRN12611000247976	Neonates with a birth weight less than 1,500 g and gestational age of 22–28 weeks in the first 7 days of age (n = 1,100)	Bovine LF 200 mg/kg/day until 34 weeks corrected age or discharge	Breast milk or formulawithout BLF until 36 weeks gestational age or discharge	**Primary outcome** 1. Incidence of sepsis or brain injury or chronic lung disease or NEC or severe retinopathy **Secondary outcome** 1. Death related to culture-proven sepsis
5	Study of Talactoferrin oral Solution for nosocomial infection in preterm infants; NCT00854633	Neonates with a birth weight between 750–1,500 g in the first 24 h of age (n = 120)	Talactoferrin alfa (recombinant human LF) (enteral) 300 mg/kg/day, twice per day, from birth to 29 days of life	Placebo (not mentioned)	**Primary outcome** 1. Reduction in incidence of culture- proven and CRP elevated LOS **Secondary outcome** 1. NEC 2. Length of stay 3. Mortality during hospitalization
6	Supplementation with lactoferrin in preterm newborns (lactoprenew); NCT01172236	Neonates with a birth weight below 1,500 g or gestational age between 23–32 weeks (n = 1,300)	Bovine LF 100 mg/day and standard therapy. Unspecified duration	Standard therapy	**Primary outcome** 1. Evaluate the antioxidant effect of LF and its ability to reduce free radicals related diseases in the newborn (neurodevelopment follow-up 12 months). **Secondary outcome** 1. Identify the panel of markers for assessing oxidative stress

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Table 1 Continued...

Serial no	Study	Population	Intervention group	Control group	Outcome
7	Effect of prebiotic or lactoferrin supplementation in formula on the gut flora of preterm infants ISRCTN71737811	Neonates of gestational age between 26–35.6 weeks admitted to the NICU or High Care Unit of the hospital (n = 80)	Standard preterm formula with addition of GOS OR Standard preterm formula with LF 1 mg/100 ml/day, for 6 weeks after start of full enteral feeds	Standard preterm formula without addition of prebiotics or LF for 6 weeks after start of full enteral feeds	**Primary Outcome** 1.Composition of gut flora 2.Incidence of infections 3.Oxidative stress and iron status **Secondary outcome** 1. Growth (head circumference, length, weight) at 6 months 2. Psychomotor development at 12 months
8	Lactoferrin for prevention of sepsis in infants (NEOLACTO); NCT01525316	Neonates with a birth weight between 500 and 2,000 g admitted to the NICU in the first 72 h of age (n = 414)	Bovine LF 200 mg/kg/day, three times per day for 8 weeks	Maltodextrin 200 mg/kg/ day, three times per day for 8 weeks	**Primary outcome** 1.First-episode of LOS or sepsis- associated death **Secondary outcome** 1.Neurodevelopment at 24 month of corrected age
9	Lactoferrin prophylaxis in VLBW; NCT01287507	Neonates with birth weight less than 1500 grams and less than 32 weeks of gestational age (n = 50)	Bovine lactoferrin 200mg/day till discharge	Oral saline daily till discharge	**Primary outcome** 1. Effect of oral LF in culture-proven sepsis 2. Effect of oral LF in NEC **Secondary outcome** 1. Safety of LF in VLBW infants: effect on feeding tolerance, abdominal distension, vomiting and gastric residuals 2. Duration of hospitalization
10	Pilot study: lactoferrin for prevention of neonatal sepsis (NEOLACTO); NCT01264536	Neonates with a birth weight between 500 and 2,500 g admitted to the NICU in the first 72 h of age (n = 190)	Bovine LF 200 mg/kg/day, three times per day for 4 weeks	Maltodextrin 200 mg/kg/ day, three times per day for 4 weeks	**Primary outcome** 1. Number of confirmed episodes of LOS **Secondary outcome** Incidence of Gram positive and Gram negative bacterial and fungal bouts of sepsis, pneumonia, diarrhoea and mortality in first month of life

Table 2 Machanism of action of lactoferrin

Microbicidal actions of lactoferrin
A. Disruption of cell membrane
B. Iron sequestration
C. Prevention of biofilm formation
D. Proteolysis of virulence factors
E. Blocks bacterial adhesion to host cells by binding to glycosaminoglycans
F. Initiates "anoikis" in which cells containing viable bacteria undergo apoptosis
G. Enhances the growth of the normal commensal bifidogenic microflora in the gut.
Anti-cancer action
A. Cell cycle arrest
B. Promotes apoptosis
C. Anti-angiogenesis
D. Antimetastasis
E. Immune modulation
F. Promotes necrosis

Source

Masson and Heremans[16] when studying ten different mammalian species reported the highest levels of LF in human breast milk. In human milk, the highest level is found in the colostrum (7 mg/mL) and 1 mg/ml in mature milk. This fall in concentration of LF is slow in preterm mother's milk.[16-18]

Composition

The composition of Bovine lactoferrin (BLF) and human lactoferrin (HLF) is almost similar with 77% of amino acid being common to both. This similarity may be responsible for efficacy of BLF in various human trials. Both of these are not digested by the enzymes of the digestive system of neonates and bind to enterocytes through their special and specific receptors. They can also be found undigested in stools of infant that are suffering from malabsorption syndromes.[19,20] LF receptors have been identified in the gastrointestinal tract, on leukocytes and macrophages, platelets, and on bacteria. The BLF is transferred from the intestine into peripheral blood in a form with intact molecular weight (80 kDa) and is localized within 10 to 20 min after oral administration in the liver, kidneys, gall bladder, spleen, and brain.[21]

Function and spectrum

LF has various properties which include its activity against various microorganism, immunomodulation and trophic activities on the developing gut. LF has broad spectrum antimicrobial activity with bacteriostatic activity against *Escherichia coli*, *Klebsiella pneumoniae*, *Streptococcus* mutans and *Candida albicans*.[22] LF and LFcin are effective against bacteria, fungi, and viruses (Table 3, Figure 1).[3] In mouse experiments, oral administration of bovine LF reduced the number of bacterial infections in the gastrointestinal tract[23] while promoting the growth of bacteria with low iron requirements such as *Lactobacillus* and *Bifidobacterium*, which are generally believed to be beneficial to the host.[24,25] Oral LF was also found to be effective against experimentally induced Urinary tract infection (UTI) and endotoxin-induced septic shock.[26,27] LF also has immune-modulatory role, ascribed to its immunotropic and anti-inflammatory effects.[28,29]

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Table 3 Spectrum of various effects of lactoferrin

Anti-microbial	
Antibacterial	**Anti-fungal**
1. *Pseudomonas aeruginosa*	1. *Candida Albicans*
2. *Haemophilusinfluenzae*	2. yeast
3. *E coli*	
4. *Helicobacter pylori*	
5. *Clostridium difficile*	
6. *Shigella Flexnieria*	
7. *Staphylococcus aureus*	
8. *Streptococcus Mutans*	
9. *Streptococcus Pneumoniae*	
10. *Aggregatibacter actinomycetemcomitans*	
11. *Yersinia enterocolitica*	
12. *Listeria monocytogenes*	
Antiviral	**Anti-cancer**
1. *Human Immunodeficiency Virus*	1. Head and neck squamous cellcarcinoma
2. *Cytomegalovirus (CMV),*	2. Breast cancer
3. *Herpes simplex virus (HSV),*	3. Colon carcinoma
4. *Hepatitis C virus (HCV),*	4. Malignant melanoma
5. *Rotavirus,*	5. bronchogenic carcinoma
6. *Poliovirus(PV),*	
7. *Respiratory syncytial virus (RSV)*	
8. *Hepatitis B virus (HBV),*	
9. *Parainfluenza virus (PIV),*	
10. *Alphavirus,*	
11. *Hantavirus,*	
12. *Human papillomavirus (HPV),*	
13. *Feline calicivirus (FCV),*	
14. *Adenovirus,*	
15. *Enterovirus 71* (EV71),	
16. *Echovirus 6,*	
17. *Influenza A virus,*	
18. *Japanese encephalitis virus,*	
19. Tomato yellow leaf curl virus(TYLCV)	

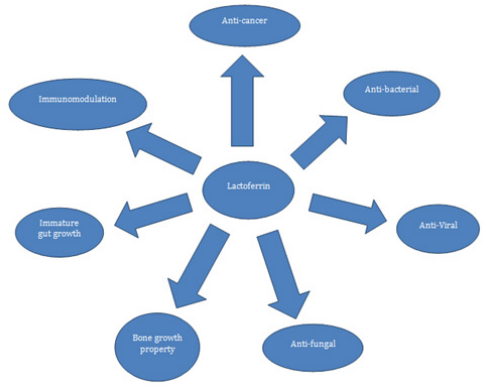

Figure 1 Figure showing spectrum of Lactoferrin.

Clinical uses of lactoferrin

Neonatal sepsis and LF

Neonatal sepsis can present in various form like blood stream infection, urosepsis or gastro-intestinal sepsis. LF or LFcin act synergistically against *E. coli* bacteria which are isolated from patients of bovine mastitis and human urinary tract infection.[30,31] Oral LF or derived peptides are also effective against *E. coli*uro-sepsis.[26] There is a presumptive hypothesis for this mechanism of action that the LF remains intact in the gastrointestinal tract and is accumulated in the blood only when the mucosal damage of GI system is seen leading to its breach in its integrity. In few preclinical trials it has been shown that recombinant HLF helps in protection in urosepsis caused by *E. coli*(O18:K1:H7).[32,33]

Manzoni et al.[7] in the first clinical study studied 472 VLBW infants that there was significant reduction in incidence of late-onset sepsis (LOS) in the BLF and BLF plus Lactobacillus rhamnosus groups (LGG groups) (9/153.$^{5.9\%}$ and 7/151.$^{4.6\%}$, respectively) when compared to the control group that was receiving placebo (29/168.$^{17.3\%}$) (RR, 0.34; 95% CI 0.17-0.70; P =.002 for BLF Vs control and RR, 0.27; 95% CI 0.12-0.60; P <.001 for BLF plus LGG Vs control).

In the secondary analysis, Manzoni et al.[34] further showed that prophylactic oral administration of BLF reduced the incidence of invasive fungal sepsis, though there was no effect reported on colonization. In other study conducted from our India, Kaur et al.[35] followed up 121 low birth weight infants and reported significant reduction in the incidence of LOS in the BLF group as compared to the placebo group.n=2/59 versus n=9/62, p=0.033). There was a trend towards lower sepsis attributable mortality in the BLF supplemented group. They also reported a trend towards reduction in fungal sepsis.

In other RCT Ochoa et al.[36] enrolled 190 infants weighing less than 2500 g at birth to either BLF or maltodextrin group. They reported reduction in the incidence of sepsis and NEC in the BLF group, though the reduction was not statistically significant.

Akim et al.[37] published their recent trial of oral LF to prevent nosocomial sepsis and NEC in premature neonates and studied effect on T-regulatory cells. They reported fewer sepsis episodes in intervention group (4.4 vs. 17.3/1,000 patient days, p=0.007) with none developing NEC, though without statistical significance.

Lactoferrin and bronchopulmonary dysplasia (BPD)

Manzoni et al.[7] reported no statistical difference in BPD, in both BLF and BLF with LGG groups after oral lactoferrin supplementation, though there was decrease in incidence in intervention group. Further research is needed to support this hypothesis.

Ventilator associated pneumonia (VAP)

Stefanescu et al.[38] in their pilot study enrolled 41 neonates, who were born before 28 weeks of gestation, and were mechanically ventilated between 7 and 10 postnatal days to see the effect of oral Biotene gel containing LF for prevention of VAP. They reported a lower rate of VAP in the Biotene group, although the difference was not statistically significant as the number was very small. Further studies are need to prove the role of LF in VAP.

Necrotizing enterocolitis (NEC)

In a recently published, randomized clinical trial conducted in 13 nursery of Italy and New Zealand, Manzoni et al.[41] evaluated bovine LF supplementation for prevention of NEC in 743 VLBW neonates. They observed these babies till discharge for any sign and symptom of NEC. The neonates were randomly allotted to three arms which received oral Bovine LF (BLF) (100 milligram/day) alone (group LF; n=247) or with LGG (at 6×109 CFU/day; group BLF + LGG; n=238), or placebo arm (Control group; n=258) after birth until day 30 of life (45 for neonates< 1000 g at birth). The primary outcome was ≥stage

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2 NEC; death and/or ≥ stage 2 NEC prior to discharge. They found out significantly reduction in incidence of NEC in both the groups of BLF and BLF + LGG.[5/247 (2.0%)] and 0/238 (0%), respectively] against the control arm.[14/258 (5.4%)] (RR=0.37; 95% CI: 0.136–1.005; p=0.055 for BLF vs. control; RR=0.00; p<0.001 (BLF + LGG vs. control). The incidence of death-and/or NEC was significantly lower in both treatment groups (4.0% and 3.8% in BLF and BLF + LGG vs. 10.1% in control; RR=0.39; 95% CI: 0.19–0.80; p=0.008. RR=0.37; 95% CI: 0.18–0.77; p=0.006, respectively). This study concluded that when compared with placebo, BLF supplementation alone or in combination with LGG reduced the incidence of ≥stage 2 NEC and of death-and/or ≥ stage 2 NEC in VLBW neonates, hence favouring the use of BLF to prevent NEC. These results are promising for prevention of NEC but it's too early to apply it to all neonates that are at risk for NEC. Results of other major studies are awaited to conclude on its effect.

Furthermore Manzoni et al.[7] in their prospective, multicentre, double-blind, placebo controlled randomized trial found out that oral LF alone did not reduce the incidence of NEC (1.9% versus 6%,p=0.09, but a significant reduction in NEC was noted with the combination of LF with LGG. The summary of all the trials conducted so far has been summarized in Table 4. There are currently no studies showing effect of LF on long term neurological outcome, neonatal jaundice, hyaline membrane disease, periventricular leucomalacia, and duration of assisted ventilation through an endotracheal tube or length of hospital stay. The other uses of lactoferrin in field of perinatology includes its role in retinopathy of prematurity, prevention of preterm labor and in treatment of iron deficiency anaemia of pregnancy.[39-42]

Table 4 Table showing various lactoferrin studies which has been completed till now

Serial No	Title	Population	Intervention group	Control group	Outcome
1	Bovine lactoferrin Supplementation for prevention of late onset sepsis in very low birth-weight neonates: a randomized trial (7).	472 very low birth weight (VLBW) neonates	Neonates received orally administered Bovine Lactoferrin (BLF) (100 mg/d) alone (n=153), BLF plus Lactobacillus rhamnosus GG (LGG) (6 x 10 9 colony forming units/d) (n=151), or placebo (n=168) from birth until day 30 of life (day 45 for neonates Less than 1000 g at birth).	Control group received placebo (2 mL of a 5% glucose solution)	The incidence of LOS significantly reduced in the BLF and BLF plus LGG groups when compared with the control group receiving placebo (RR, 0.34; 95% CI, 0.17-0.70; P= 0.002 for BLF vs. control and RR, 0.27; 95% CI, 0.12-0.60; P< 0.001 for BLF plus LGG vs. control). The incidence of invasive fungal infection (IFI) was significantly decreased in BLF (P = .002) and P =0.02 in BLF plus LGG group. The progression rate colonization-infection was significantly lower in the BLF groups.
2	Efficacy of bovine lactoferrin supplementation in preventing late onset sepsis in low birth weight neonates: randomised placebo controlled clinical trial (37).	121 low birth weight (less than 2000 grams) neonates	Bovine Lactoferrin [BLF] (n = 59) was supplemented daily from first to 28th day of life.	Control group (n= 62) received placebo daily from first to 28th day of life.	Incidence of first episode of culture proven LOS significantly lower in the BLF group. They found that incidence of first episode of culture proven LOS was significantly lower in the BLF group than in the placebo group [2/59 (3.4%) versus 9/62 (14.5%); p = 0.033]. The sepsis attributable mortality after 72 hours of life was comparable among the BLF supplemented and placebo group [0/59 (0) versus 5/62 (8.1%); p = 0.058]
3	Lactoferrin for prevention of sepsis in Peruvian neonates (38)	190 low birth weight (LBW) neonates	BLF was given enterally at 200 mg/d in 3 divided doses over the first 4 weeks of life.	Control group received placebo (maltodextrin) enterally at 200 mg/d in 3 divided doses over the first 4 weeks of life	There was a decreasing trend in incidence of sepsis in the BLF group [12/95 (12.6%)] compared to the placebo group [22/95 (23.2%)]. For babies weighing less than 1500 g at birth, the occurrence of NEC was 20% in the BLF group (8/40) versus 40% in the control group (16/40).
4	Bovine lactoferrin supplementation for prevention of necrotizing enterocolitis in very-low-birth-weight neonates: a randomized clinical trial(41)	743 VLBW neonates	Neonates received orally administered Bovine Lactoferrin (BLF) (100 mg/d) alone (n=247), BLF plus Lactobacillus rhamnosus GG (LGG) (6 x 10 9 colony forming units/d) (n=238), or placebo (n=258) from birth until day 30 of life (day 45 for neonates Less than 1000 g at birth).	Control group received placebo	NEC incidence was significantly lower in groups BLF and BLF + LGG than in controls with (RR = 0.37; 95% CI: 0.136-1.005; p = 0.055 for BLF vs. control; RR = 0.00; p < 0.001 for BLF + LGG vs. control). The incidence of death- and/or-NEC was significantly lower in both treatment groups (BLF and BLF + LGG vs. control; RR = 0.39; 95% CI: 0.19-0.80; p = 0.008. RR = 0.37; 95% CI: 0.18-0.77; p = 0.006, respectively).
5.	A pilot study of Biotene OralBalance® gel for oral care in mechanically ventilated preterm neonates (40)	41 neonates born before 28 weeks of gestation and mechanically ventilated between 7 and 10 postnatal days.	Timed oral care with Biotene OralBalance® gel	Timed oral care with sterile water	No significant group differences in mortality or short-term outcomes, except length of hospital stay which was significantly shorter in the Sterile water group (p = 0.02). Lower rate of VAP was found in the Biotene group, although the difference was not statistically significant p = 0.16).
6	Oral lactoferrin to prevent nosocomial sepsis and NEC of premature neonates and effect on T-regulatory cells (39).	50 neonates either VLBW or born before 32 weeks	200 mg LF daily till discharge	Control group received placebo. Third group healthy neonates (16)	Fewer sepsis episodes were observed in LF-treated infants p = 0.007) with none developing NEC, without statistical significance.

LOS, Late onset sepsis; LBW, Low Birth Weight; NEC, Necrotizing Enterocolitis; VLBW, Very Low Birth Weight

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Conclusion

Lactoferrin is a defence protein with diverse physiological functions. It has potent antimicrobial action against bacteria, fungi, viruses, and even some antibiotic-resistant strains. It has bacteriostatic, bactericidal, and anti-adhesion effects. Furthermore it's other property of anti-inflammation helps in protection of neonates from the sepsis caused by the pathogenic organism. Lactoferrin is gaining evidence for its role in Neonatal sepsis although still much work needs to be done to ensure safety. It may soon come as the wonder molecule to attenuate the morbidity and mortality resulting from devastating neonatal sepsis and NEC.

Acknowledgments

None.

Conflicts of interests

The authors declare that there are no conflicts of interest.

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