Bovine Lactoferrin Supplementation for Prevention of Late-onset Sepsis in very Low-Birth-Weight Neonates

Khalid M. AlFaleh
Associate professor and Consultant Neoantologist, King Saud University, Riyadh, Saudi Arabia. E-mail: kfaleh@ksu.edu.sa

CONTEXT

Late-onset sepsis affects 21% of VLBW infants and is associated with increased mortality and long-term neurosensory impairment. Lactoferrin is the major whey protein in Mammalian milk and is quite important in innate host defenses. Bovine Lactoferrin anti-infective ability has been shown *in vitro* and in animal models. Its activity is enhanced by the addition of Lactobacillus GG in animal models.

MATERIALS AND METHODS

Multicenter randomized controlled trial in 11 neonatal intensive care units in Italy.

Population

Inclusion

VLBW infants younger than 3 days of age.

Exclusion

Lack of parental consent;
Ongoing antifungal prophylaxis;
Early-onset sepsis;
Evidence of liver failure (threefold increase in liver enzymes).

Intervention

Three groups

Lactoferrin group

BLF (100 mg/d) (LF100; Dicofarm SpA, Rome, Italy) alone.
Lactoferrin + Lactobaccilus GG
BLF and Lactobacilus GG (6 × 109 colony-forming units/d) (Dicoflor 60, Spa Dicofarm).

Control

Placebo (2 cc of D5% glucose solution).
Treatment lasted 6 weeks for infants <1000 g or 4 weeks for infants with birth weight 1001–1500 g or until discharge. Breast milk was encouraged.

Outcomes

Primary

To evaluate the effectiveness of BLF alone or BLF plus LGG in the prevention of the first episode of late-onset sepsis of bacterial or fungal origin.

Secondary

The incidence of gram-positive/gram-negative bacterial and fungal sepsis, mortality before discharge (overall and sepsis attributable), incidence of urinary tract infections, fungal colonization, progression from fungal colonization to invasive fungal infection (IFI), stage 2 or greater necrotizing enterocolitis, threshold retinopathy of prematurity, severe (grades 3–4) intraventricular hemorrhage, bronchopulmonary dysplasia, alteration of liver function, and adverse effects or intolerance.

Allocation

Computer-generated random sequence allocation.

Blinding

Blinded, clinical, and research staff were unaware of group assignment. Pharmacy staff prepared the three groups based on randomization lists.

Follow-up

Infants were followed till death or discharge; 100% follow-up rate.

RESULTS

In all, 151, 153, and 168 infants were enrolled in the BLF and BLF + LGG and control groups, respectively. The mean birth weight was 1100. The mean gestational age was 29

Table 1: Main results

Result	BLF (*n*=153)	BLF + LGG (n=151)	Control (*n*=168)	RR (95% CI)	*P* Value
Bacterial and fungal late-onset sepsis; total late- onset sepsis (total=45)	9/153 (5.9)	7/151 (4.6)	29/168 (17.3)	0.34 (0.17–0.70)	0.002
Invasive fungal infection total	0/153 (0)	2/151 (1.3)	9/168 (5.4)	–	0.004
All-cause mortality	4/153 (2.6)	6/151 (4.0)	12/168 (7.1)	0.37 (0.12-1.11)	0.07
Mortality attributable to sepsis	0/153 (0)	1/151 (0.7)	8/168 (4.8)	–	0.008

Table 2: Secondary out comes

	BLF	BLF + LGG	Control	BLF vs control
Threshold ROP requiring surgery	6/153 (3.9)	13/151 (8.6)	19/168 (11.3)	0.02
NEC > stage 2	3/153 (1.9)	0/151 (0)	10/168 (6.0)	0.09

weeks. No differences were noted in baseline characteristics, risk factors for sepsi,s and feeding type or regimen used in all three groups.

COMMENTARY

The trial by Manzoni *et al*. is the only study addressing the effectiveness of Lactoferrin supplementation in prevention of late-onset sepsis in the preterm host. Lactoferrin supplementation reduced the incidence of sepsis with a NNT of 9. There seems to be a synergistic effect through the addition of probiotics to Lactoferrin. This reduction in late-onset sepsis was more pronounced in ELBW infants when compared with infants between 1000 to 1500 g with a NNT of 4.

Previous 16 randomized controlled trials for the use of probiotics in preterm infants showed a significant reduction in severe NEC, however with a minor statistically insignificant effect in prevention of late-onset sepsis. The use of Lactoferrin and probiotics group in Manzoni *et al.* trial eliminated severe NEC, which might suggest a potential synergy of these two interventions.

The optimum time of prophylaxis with Lactoferrin seems to be the first 3 days of age. The effective duration of therapy is still to be explored. A trend toward a decrease in all-cause mortality was also noted. Lactoferrin was well tolerated with no apparent adverse side effects.

These results are very encouraging to neonatal practitioners; however, it is still to be confirmed and refined through further trials.

Abstracted from

Manzoni P, Rinaldi M, Cattani S, Pugni L, Romeo MG, Messner H, *et al.* Bovine lactoferrin supplementation for prevention of late-onset sepsis in very low-birth-weight neonates: A randomized trial. JAMA 2009;302:1421-8.

REFERENCES

1. Alfaleh K, Anabrees J, Bassler D, Al-Kharfi T. Probiotics for prevention of necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev 2011;3:CD005496.
2. Pammi M, Abrams SA. Oral lactoferrin for prevention of sepsis and necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev 2011;10:CD007137.