Bovine Lactoferrin Prevents Invasive Fungal Infections in Very Low Birth Weight Infants: A Randomized Controlled Trial

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**CONTEXT**

Invasive fungal infections in the preterm are responsible for increased mortality and long-term morbidity in the preterm infants. Colonization (occur in 46% of VLBW infants) is a usual precedent of invasive disease. Ten percent of colonized infants progress to invasive disease. Fluconazol prophylaxis has been shown to effectively decrease the rates of invasive fungal infection in VLBW infants; however, concerns with regard to long-term safety and emergence of resistance still exist. Bovine lactoferrin has been shown to decrease the rates of late onset sepsis through its documented antinfective properties. This study is a subgroup analysis of the previously published paper in JAMA with a focus of lactoferrin role in decreasing the rates of fungal colonization and invasive disease in VLBW infants.

**METHODS**

This is a secondary analysis of the data obtained during a multicenter RCT developed in Italy in the years 2006–2007.

Multi-center 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 (three-fold increase in liver enzymes)

**Intervention**

**Three groups**

**Lactoferrin group**
BLF (100 mg/d) (LF100; DicofarmSpA, Rome, Italy) alone

**Lactoferrin + Lactobacillus GG**
BLF (same dose as above) and Lactobacilus GG (6×10^9 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.

Minimal enteral feeding with small amounts of maternal milk or formula (10 ml/kg per day) was initiated at DOL 2. Cautious volume advancements were performed by adding 15 ml/kg per day. Parenteral nutrition was started at DOL...
2 and continued until enteral feeding reached 150 mL/kg per day.

Outcomes

Primary
Rates of fungal colonization and invasive fungal infection (IFI). Systematic surveillance for detection of fungal colonization was performed through clinical and weekly surveillance cultures (>3 cultures per week).

Secondary
Intensity of fungal colonization, rates of progression from colonization to invasive disease, frequency of single fungal species in each group and IFI-related mortality.

Allocation
Computer-generated random sequence allocation. This was a preplanned secondary analysis.

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
One hundred and fifty-one, 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 29.5 weeks. No differences were noted in baseline characteristics, risk factors for sepsis or fungal infections and feeding type or regimen used in all three groups.

Table 1: Outcome data

|                          | LF     | LF + LGG | Control | LF Versus Control, P |
|--------------------------|--------|----------|---------|----------------------|
| Total IFI, n=17 (%)      | 1/153  | 3/151    | 13/168  | 0.08                 |
| IFI in extremely low birth weight neonates (%) | 1/53   | 3/54     | 9/60    | 0.13                 |
| Overall fungal colonization, at least 1 site (%) | 27/153 | 25/151  | 31/168  | 0.96                 |
| Mortality attributable to IFI (%) | 0/153  | 0/151    | 2/168   | –                    |
| Threshold retinopathy of prematurity, requiring surgery (%) | 6/153  | 13/151   | 19/168  | 0.02                 |
| NEC, stage II or greater (%) | 3/153 | 0/151    | 10/168  | 0.09                 |
| Death or NEC, stage II or greater (%) | 7/153 | 7/151    | 18/168  | 0.06                 |

COMMENTARY

This secondary analysis of a previously published paper by Manzoni et al. provides a very interesting data of the role of bovine Lactoferrin in prophylaxis against invasive fungal infections in the preterm host. The data presented augments previously known antinfective ability of Lactoferrin in the prevention of late onset sepsis. This effect of Lactoferrin was more pronounced when ELBW infants are included with a number needed to treat of 7. The data does not suggest any additional synergistic effect when probiotics are added to Lactoferrin. According to this data, Lactoferrin has the same impact of prevention IFI as compared to fluconazole.[2,3] Although the death rate in Lactoferrin group was one-third of the control one, this did not reach statistical significance mostly due to lack of power. Death attributable to IFI was not different; however, the numbers are too low to make firm conclusion.

Although, the data is robust, supported by pathophysiologic rationale; clinicians should take the results of this trial by caution and await further data to support these findings.

Abstracted from
Manzoni P, Stolfi I, Messner H, Cattani S, Laforgia N, Romeo MG, et al. Bovine lactoferrin prevents invasive fungal infections in very low birth weight infants: A randomized controlled trial. Pediatrics 2012;129:116-23.

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