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Lactoferrin reduces febrile neutropenia in children receiving chemotherapy for hematologic malignancies: a randomized, placebo-controlled trial

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For original data, please contact the corresponding authors. Individual participant data will not be shared.

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Trial registration

ClinicalTrials.gov identifier: NCT07113314

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Authorship Contributions

N.D developed the concept, performed the study, analyzed data and wrote the manuscript; D.Z. performed the study, analyzed data and wrote the manuscript; E.M. analyzed data, took care for patients and helped writing the manuscript; G.T., C.K. and L.S. performed the biostatistical analyses, created the figures, and helped writing the manuscript; P.M., K.P.,V.V.,A.C., N.G., R.M.,R. D.S., S.R., performed the study and took care for patients; M.Z. and S.C. critically revised the manuscript and analyzed data; all authors have critically revised and approved the final version of the manuscript.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Febrile neutropenia (FN) is one of the most frequent and clinically significant complications of intensive chemotherapy for pediatric hematologic malignancies, occurring in up to 25% of cases [1]. FN can lead to bloodstream infection (BSI), septic shock, and treatment delays. In addition to its direct morbidity, FN results in prolonged hospitalization, increased healthcare costs, and overuse of antibiotics [2]. Notably, exposure to systemic antibiotics during FN episodes increases the risk of microbial resistance, antibiotic-related adverse events, and disruption of the gut microbiota (GM)[3]. Recent evidence indicates that the GM also plays a pivotal role in the pathogenesis of FN. Chemotherapy-induced mucosal injury leads to a loss of microbial diversity and an overgrowth of pathobionts, such as Enterobacteriaceae, Enterococcaceae, and Akkermansia spp., which can facilitate bacterial translocation and trigger systemic inflammation[4]. Therefore, strategies that preserve a healthy microbiota may offer an effective, antibiotic-sparing approach to infection prevention.

Lactoferrin (Lf) is an 80 kDa cationic glycoprotein secreted by epithelial cells and neutrophil granules and is abundant in colostrum and other mucosal secretions. Lf exhibits antimicrobial, anti-inflammatory, and immunomodulatory properties, acting through mechanisms such as iron sequestration, disruption of bacterial membranes, inhibition of biofilm formation, and modulation of cytokine release (including IL-6, IL-10, and TNF-α) [5,6]. Notably, oral bovine Lf (bLf), which shares 70% sequence homology with the human protein, has demonstrated clinical benefits in reducing sepsis and necrotizing enterocolitis in preterm infants [7,8] as well as in mitigating infectious diarrhea and recurrent respiratory or urinary infections in children [9].

Given these properties, we hypothesized that oral bLf could reduce the incidence of FN and infections during induction chemotherapy in children with acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), or non-Hodgkin lymphoma (NHL). These diseases are all characterized by profound and prolonged neutropenia, mucositis, and gut microbiota dysbiosis[4].

We conducted a prospective, multicenter, randomized, double-blind, placebo-controlled trial (NCT07113314) among 9 centers of the Italian Association of Pediatric Hematology and Oncology (AIEOP). The study was approved by the Ethics Committee of Fondazione IRCCS Policlinico San Matteo, Pavia, Italy (Protocol 20160001176), and ratified by local ethics boards.

Eligible patients were aged >1 month and <21 years, receiving first-line induction chemotherapy for ALL, AML, or NHL according to AIEOP protocols, with written informed consent signed from parents or guardians. Exclusion criteria included gut colonization with multidrug-resistant organisms, prior chemotherapy, or inability/refusal to take oral medication.

Patients were randomized 1:1, stratified by center, using blocks of different size (2–6). Random allocation sequence was generated using the software STATA 14.0 (StataCorp., College Station, TX, USA). Allocation was managed by an Interactive Web Response System (REDCap-based).

The experimental arm received oral bovine lactoferrin (Mosiac®, Pharmaguida, Rome, Italy) 200 mg once daily for 8 weeks, corresponding to the induction chemotherapy period. The control arm received identical placebo capsules. Both products were indistinguishable in appearance, ensuring that study staff, patients, and families remained blinded to group allocation. Capsule can be opened and the powder swallowed with few milliliters of liquids. Adherence was monitored through patient diaries and capsule counts. The purity of bLf, checked by SDS-PAGE and silver nitrate staining, was about 98%. The bLf iron saturation was about 10%. All supportive therapies were according to local practices, and the use of antibiotic prophylaxis was recorded in the electronic CRF.

The primary endpoint was the incidence of FN with absolute neutrophil count [ANC] <0.1 G/L over 90 days. Secondary endpoints included incidence of FN with ANC <0.5 G/L, fever of unknown origin (FUO), microbiologically documented infections (MDI), and safety.

This preliminary efficacy study aimed to exclude, using a one-sided 80% confidence interval, that the difference in FN incidence between the treated and control groups was less than 5%.

Patients were analyzed according to their randomized treatment group, using intention-to-treat analysis. Incidence rates were compared by Cox regression and Kaplan–Meier analysis, with results expressed as hazard ratios (HRs). The number needed to treat (NNT) was calculated as the inverse of cumulative incidences difference between the two treatment arms at specific points in time derived from the Kaplan-Meier curves.

Between January 2017 and June 2020, 156 patients were enrolled: 79 in the bLf arm and 77 in the placebo arm, respectively (Supplementary Figure S1). Median age was 6 years (range 1–17) in the bLf group and 7 years (1–20) in placebo. Diagnoses included ALL (117/156, 75.0%), AML (17/156, 10.9%), and NHL (22/156, 14.1%). At enrollment, there were no between-arm differences in clinical and demographic data (Table 1).

Over 90 days, FN with ANC < 0.1 G/L occurred in 33/79 patients (41.8%) in the bLf arm versus 40/77 (51.9%) in placebo. Accounting for time-to-event in a Cox regression analysis, the incidence rate was significantly lower in the bLf arm (4.4 vs. 6.9 cases per 100 person-weeks), corresponding to a 37% risk reduction (HR 0.63; 80% CI 0.47–0.85; p = 0.05) (Figure 1). The NNT at 90 days was 8, meaning one FN event was prevented for every eight patients treated. The NNTs at weeks 4, 6, and 8 were 7, 8, and 9, respectively.

When considering FN with ANC < 0.5 G/L, the incidence was still lower in the bLf group (58.2%) compared to placebo (63.6%), and in a Cox regression model the incidence rate of this event tended

(p=0.10) to be lower (-29%) in the bLf group (7.1 cases per 100 persons-week) as compared to the placebo group (9.9 cases per 100 persons-week) (bLf versus placebo, hazard ratio: 0.71, 80% CI: 0.55-0.93) (Supplementary Figure S2). At 4, 6, and 8 weeks, the NNT values for the incidence of FN < 0.5 G/L were 10, 10, and 11, respectively.

During the 90-day follow-up, FUO occurred in 36/77 (46.7%) placebo versus 32/79 (40.5%) bLf patients—a 19% lower total number of episodes (43 vs 53). The 90-day cumulative incidence was 50% (95% CI 38–62) in placebo and 42% (31–53) in bLf (p = 0.20; NNT = 12) (Figure 2A).

MDI were diagnosed in 11/77 (14.3%) placebo and 8/79 (10.1%) bLf patients (p = 0.40) (Figure 2B). The distribution of pathogens among blood cultures was comparable between groups (Supplementary Table S1). Incidence of Clostridioides difficile, vancomycin-resistant Enterococcus, or multidrug-resistant bacteria was too low for analysis. No treatment-related adverse events (AE) were observed; overall AE incidence was not statistically different between groups (Placebo Arm, 18 AE in 14 patients; bLf Arm, 26 AE in 10 patients).

This is the first randomized, double-blind, placebo-controlled trial providing evidence that oral bLf may reduce FN incidence during induction chemotherapy in children with hematologic malignancies. Patients receiving bLf experienced a 37% lower rate of FN and a consistent trend toward fewer FUO episodes, without safety concerns. To our knowledge, this is the first randomized trial evaluating bLf as a preventive strategy for FN in pediatric oncology. The effect size observed exceeded initial expectations and aligns with prior evidence of LF's protective role against sepsis in preterm infants[10]. Lf's antimicrobial actions are multifaceted. Through iron sequestration, it deprives pathogens of an essential growth factor, limiting proliferation of Gram-positive and Gram-negative bacteria and fungi. In addition, Lf binds bacterial lipopolysaccharides and lipoteichoic acid, disrupts membranes, inhibits adherence and internalization into host cells [11].

Beyond direct antimicrobial effects, Lf exerts anti-inflammatory and immunomodulatory actions. It modulates cytokine production (IL-1β, IL-6, TNF-α), promotes IL-12-mediated Th1 responses, enhances NK and T-cell activity, and reduces oxidative stress via iron chelation[12]. These effects may help explain why, in our cohort, the incidence of MDI and bacteremia was similar between groups, whereas the incidence of FUO was reduced in bLf-treated patients—particularly during the first six weeks of treatment. This pattern is reflected in the Kaplan–Meier cumulative-incidence curve, which mirrors the trend observed for FN. The origin of FUO is often noninfectious and may be driven by cytokine-mediated mechanisms.

Another mechanism may involve preservation of healthy gut microbiota, as found in an ancillary study of our cohort[13], where bLf prevented chemotherapy-induced loss of microbial diversity, reduced pathobionts (Enterobacteriaceae, Akkermansia), and maintained butyrate-producing

commensals. These changes are consistent with prior work showing that Enterococcus and Akkermansia expansion predicts FN and infection risk in leukemia patients[4]. Maintenance of butyrate producers supports mucosal integrity, modulates inflammatory responses, and decreases oxidative stress, potentially mediating the clinical benefit of bLf.

Future studies should explore extended supplementation throughout intensive chemotherapy, weight-adjusted dosing, and evaluation in higher-risk settings such as relapsed leukemia or hematopoietic stem cell transplantation. Combining bLf with other microbiota-modulating interventions (e.g., prebiotics or postbiotics) may further enhance efficacy[15].

In conclusion, oral bLf supplementation during induction chemotherapy may reduce FN incidence in children with acute leukemia or lymphoma, without adverse effects. By bridging antimicrobial, anti-inflammatory, and microbiota-stabilizing mechanisms, bLf may represent a promising, safe, and non-antibiotic strategy for preventing FN in high-risk pediatric patients. These encouraging findings warrant confirmation in a larger, adequately powered phase III trial.

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Table 1 Patients' characteristics by study arms.

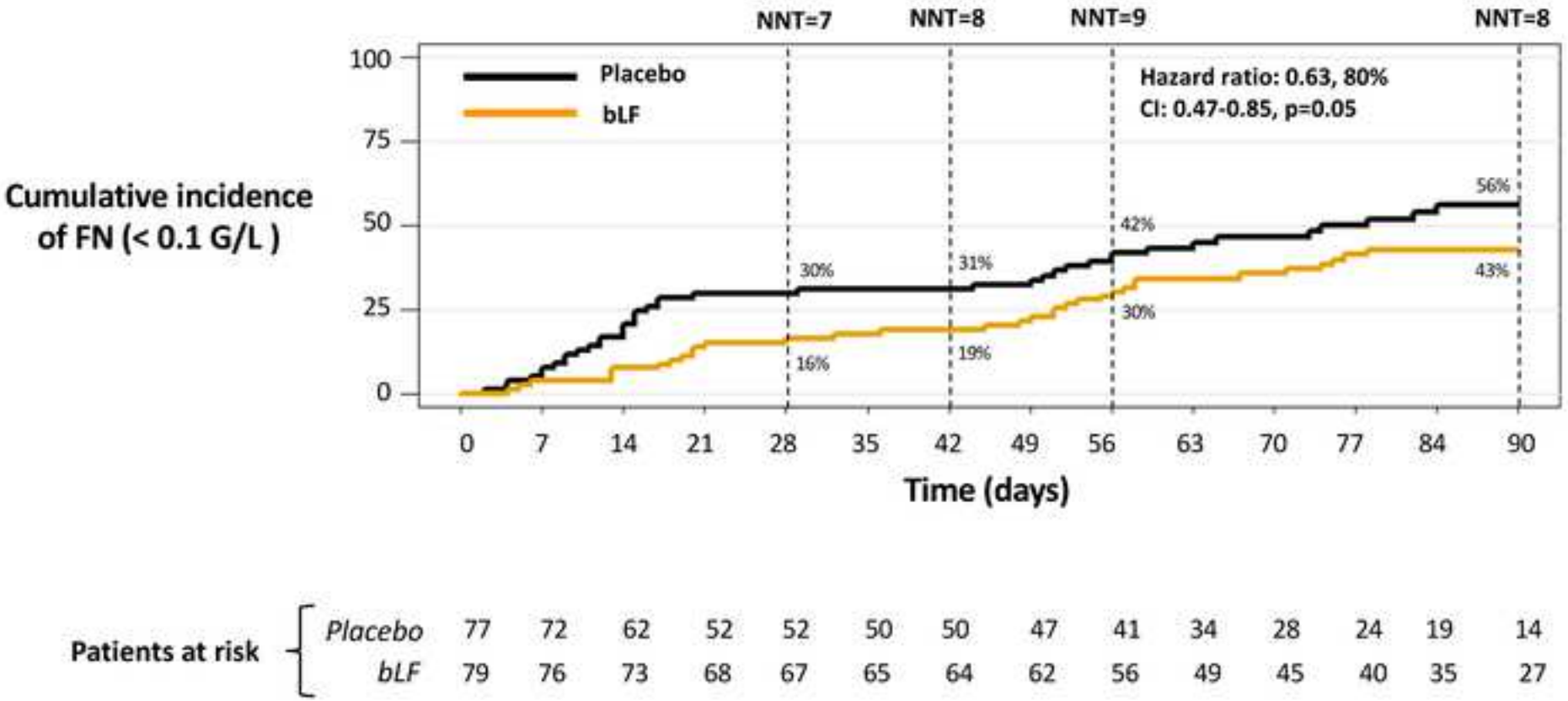
Characteristics	**Patients**		**Total**
	Placebo group (n=77)	bLF group (n=79)	n=156
Sex			
Male, n (%)	42 (54.6)	49 (62.0)	91 (58.3)
Female, n (%)	35 (45.5)	30 (38.0)	65 (41.7)
Age at random			
Median, years (min-max)	7 (1-20)	6 (1-17)	6 (1.0-17)
Underlying diseases			
ALL, n (%)	56 (72.7)	61 (77.2)	117 (75.0)
AML, n (%)	9 (11.7)	8 (10.1)	17 (10.9)
NHL, n (%)	12 (15.6)	10 (12.6)	22 (14.1)

Legend: ALL= Acute Lymphoblastic Leukemia; AML= Acute Myeloid Leukemia; bLF= bovine Lactoferrin; NHL= Non Hodgkin Lymphoma

Figure 1. Cumulative Incidence of FN by study arms
Legend: bLF= bovine Lactoferrin; FN= Febrile Neutropenia.

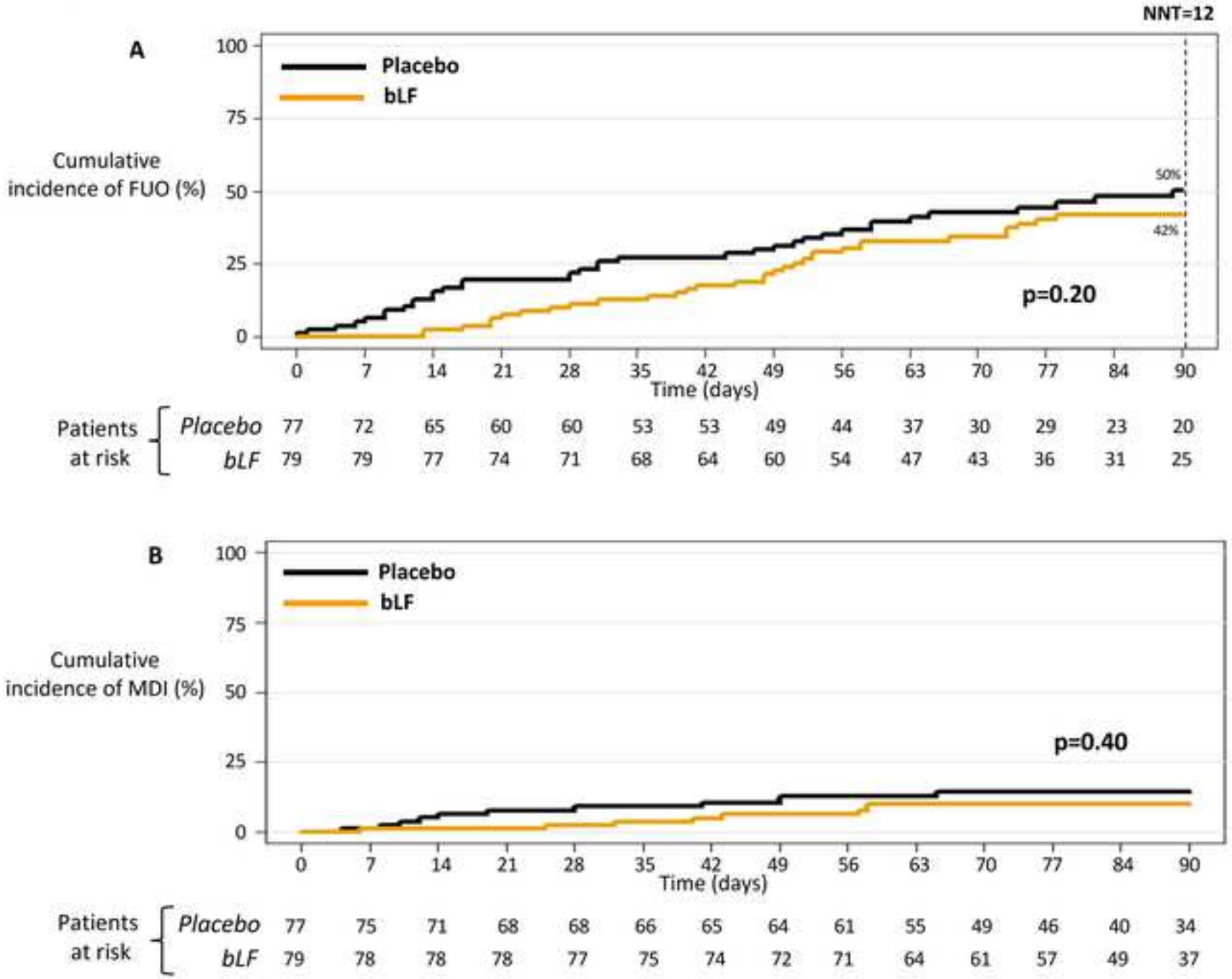
Figure 2. Cumulative Incidence of FUO and MDI by study arms.
Panel A shows the cumulative incidence of FUO across study arms, and in Panel B it is reported the cumulative incidence of MDI in the two groups.
Legend: bLF= bovine Lactoferrin; FUO= Fever of Unknown Origin; MDI =Microbiologically documented infection.

Figure 1



Patients at risk															
Placebo	77	72	62	52	52	50	50	47	41	34	28	24	19	14
bLF	79	76	73	68	67	65	64	62	56	49	45	40	35	27

Figure 2

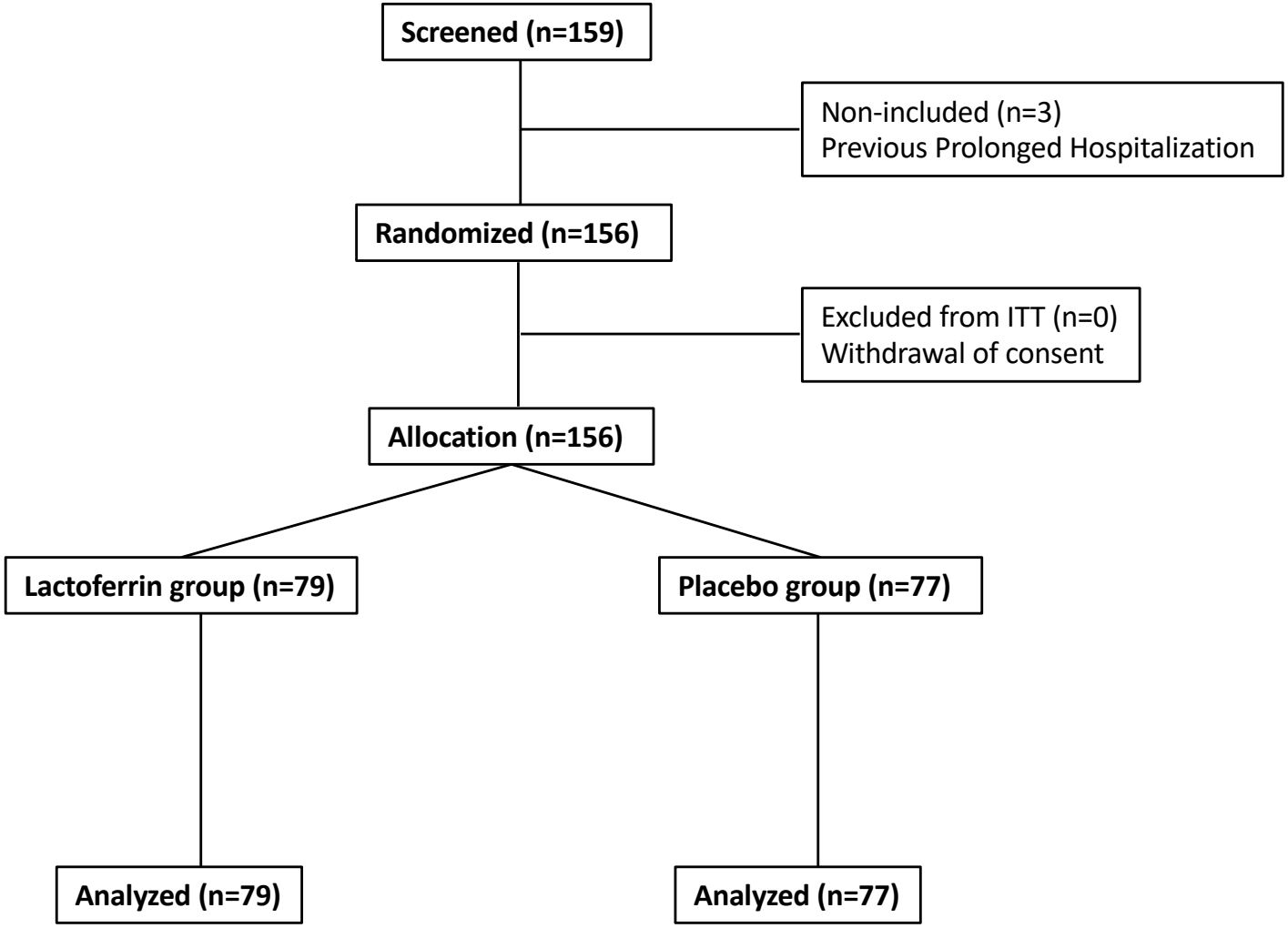


Supplementary Table S1 Blood cultures result in the two study arms.

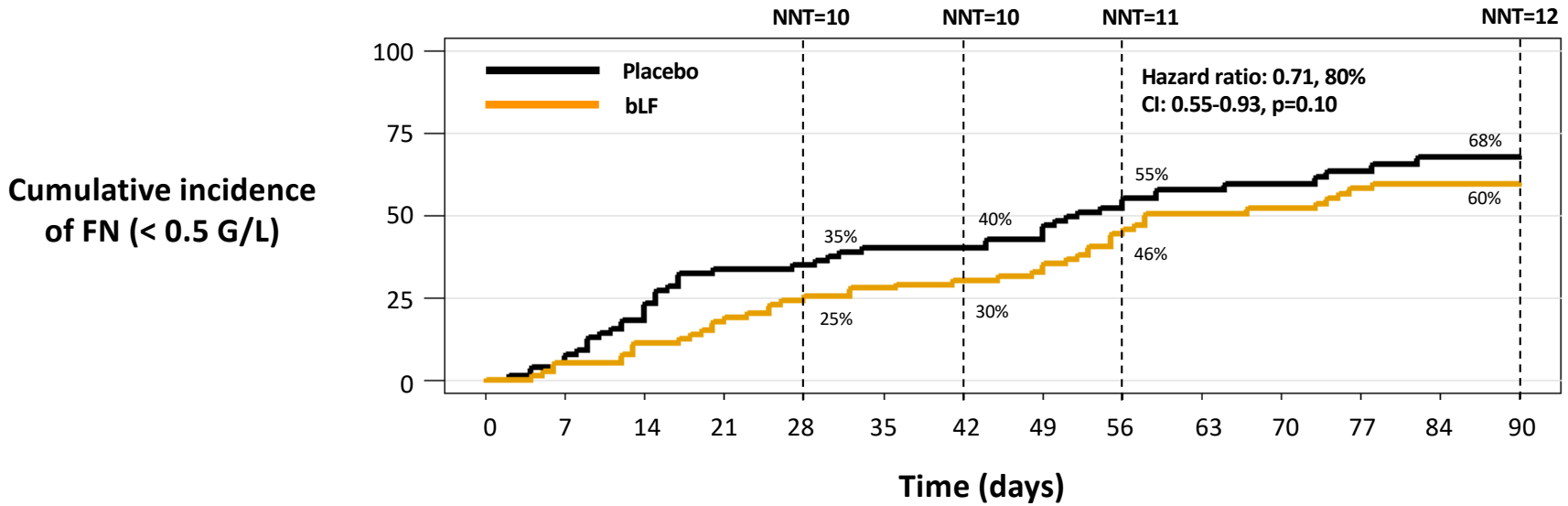
	Treatment group	
	Placebo	**bLf arm**
Pathogen		
Pseudomonas aeruginosa	3	3
Escherichia Coli	1	2
Staphylococcus haemoliticus	3	0
Staphylococcus epidermidis	0	3
Staphylococcus hominis	0	1
Streptococcus mitis	0	1
Streptococcus oralis	1	0
Streptococcus mitis/oralis	1	0
Enterococcus gallinarum	0	1
Enterococcus faecium	0	1
Brevibacterium	1	0
Klebsiella Pneumoniae	1	0
Klebsiella varicola	0	1
Klebsiella Pneumoniae + Staphylococcus epidermidis	1	0
Pseudomonas aeruginosa + Staphylococcus haemoliticus	1	0
Total	**13**	**13**

Supplementary Figure S1. Screened patients, allocation ad drop-out

Supplementary Figure S2. CI of FN < 0.5 G/L by study arms



Supplementary Figure S1



Supplementary Figure S2