Exposure to Gastric Acid Inhibitors Increases the Risk of Infection in Preterm Very Low Birth Weight Infants but Concomitant Administration of Lactoferrin Counteracts This Effect

Paolo Manzoni, MD[1], Ruben García Sánchez, MD[2], Michael Meyer, MD[3], Ilaria Stolfi, MD[4], Lorenza Pugni, MD[5], Hubert Messner, MD[6], Silvia Cattani, MD[7], Pasqua Maria Betta, MD[8], Luigi Memo, MD[9], Lidia Decembrino, MD[10], Lina Bollani, MD[10], Matteo Rinaldi, MD[11], Maria Fioretti, MD[1], Michele Quercia, MD[12], Milena Maule, PhD[13], Elena Tavella, MD[1], Alessandro Mussa, MD[1], Chryssoula Tzialla, MD[10], Nicola Laforgia, MD[12], Fabio Mosca, MD, PhD[5], Rosario Magaldi, MD[11], Michael Mostert, MD, PhD[14], and Daniele Farina, MD[1], on behalf of the Italian Task Force for the Study, and Prevention of Neonatal Fungal Infections and the Italian Society of Neonatology*

Objective To investigate whether exposure to inhibitors of gastric acidity, such as H2 blockers or proton pump inhibitors, can independently increase the risk of infections in very low birth weight (VLBW) preterm infants in the neonatal intensive care unit.

Study design This is a secondary analysis of prospectively collected data from a multicenter, randomized controlled trial of bovine lactoferrin (BLF) supplementation (with or without the probiotic *Lactobacillus rhamnosus* GG) vs placebo in prevention of late-onset sepsis (LOS) and necrotizing enterocolitis (NEC) in preterm infants. Inhibitors of gastric acidity were used at the recommended dosages/schedules based on the clinical judgment of attending physicians. The distribution of days of inhibitors of gastric acidity exposure between infants with and without LOS/NEC was assessed. The mutually adjusted effects of birth weight, gestational age, duration of inhibitors of gastric acidity treatment, and exposure to BLF were controlled through multivariable logistic regression. Interaction between inhibitors of gastric acidity and BLF was tested; the effects of any day of inhibitors of gastric acidity exposure were then computed for BLF-treated vs -untreated infants.

Results Two hundred thirty-five of 743 infants underwent treatment with inhibitors of gastric acidity, and 86 LOS episodes occurred. After multivariate analysis, exposure to inhibitors of gastric acidity remained significantly and independently associated with LOS (OR, 1.03; 95% CI, 1.008-1.067; $P = .01$); each day of inhibitors of gastric acidity exposure conferred an additional 3.7% odds of developing LOS. Risk was significant for Gram-negative ($P < .001$) and fungal ($P = .001$) pathogens, but not for Gram-positive pathogens ($P = .97$). On the test for interaction, 1 additional day of exposure to inhibitors of gastric acidity conferred an additional 7.7% risk for LOS ($P = .003$) in BLF-untreated infants, compared with 1.2% ($P = .58$) in BLF-treated infants.

Conclusion Exposure to inhibitors of gastric acidity is significantly associated with the occurrence of LOS in preterm VLBW infants. Concomitant administration of BLF counteracts this selective disadvantage. *(J Pediatr 2017;■■:■■-■■).*

Trial registration isrctn.org: ISRCTN53107700.

Despite increased awareness and adoption of prophylactic measures, infections in preterm very low birth weight (VLBW) neonates in the neonatal intensive care unit (NICU) are frequent and are associated with substantial short-and long-term morbidity, increased health costs, and poor neurosensorial and neurodevelopmental outcomes in survivors.[1-3] Accordingly,

BLF	Bovine lactoferrin
FOS	Fructo-oligosaccharides
H2B	H2 blocker
LGG	*Lactobacillus rhamnosus* GG
LOS	Late-onset sepsis
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
PPI	Proton-pump inhibitor
RCT	Randomized controlled trial
VLBW	Very low birth weight

From the [1]Neonatology and NICU, S Anna Hospital, AOU Città della Salute e della Scienza, Torino, Italy; [2]Neonatology and NICU, Complejo Asistencial Universitario de Salamanca, Salamanca, Spain; [3]Neonatology and NICU, Middlemore Hospital, Auckland, New Zealand; [4]Neonatology, Azienda Ospedaliera Universitaria Policlinico Umberto I, Rome; [5]NICU, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan; [6]Neonatology and NICU, Ospedale Regionale, Bolzano/Bozen; [7]NICU, University of Modena and Reggio Emilia, Modena; [8]NICU, Azienda Ospedaliera Universitaria Policlinico di Catania; [9]UOC di Pediatria e Patologia Neonatale, Ospedale San Martino, Belluno; [10]Patologia Neonatale, Fondazione IRCCS Policlinico San Matteo, Pavia; [11]Neonatology, Ospedali Riuniti, Foggia; [12]Cancer Epidemiology Unit, University of Turin, Department of Medical Sciences, Torino, Italy; [13]Cancer Epidemiology Unit, University of Turin, Torino; and [14]Department of Pediatrics, University of Turin, Torino, Italy

*List of additional members of the Italian Task Force for the Study and Prevention of Neonatal Fungal Infections is available at www.jpeds.com (**Appendix**).

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strategies that aim to prevent rather than treat infections have been developed, and include hygiene measures, use of central venous catheter infection prevention practices, pharmacologic and nutritional prophylaxis, and medical stewardship.[4,5]

Despite the lack of class A evidence, inhibitors of gastric acid, such as H2 blockers (H2B; eg, ranitidine, cimetidine) and proton-pump inhibitors (PPIs; eg, omeprazole) have been widely used in recent decades in preterm infants to prevent upper gastrointestinal bleeding and to manage oral feeding intolerance or gastroesophageal reflux.[6]

Gastric acidity is a primitive, innate defensive system that decreases the density of ingested microorganisms passed pathogens from the stomach to the gut, hence decreasing the burden of microorganisms in the gut, which can disseminate into the bloodstream via an immature and leaky gut barrier.[7] Inhibitors of gastric acidity increase stomach pH, thereby decreasing the gastric acid barrier and potentially increasing the risk of systemic infection and necrotizing enterocolitis (NEC).[8-13]

An association between exposure to inhibitors of gastric acidity and NICU infections has been suggested in a limited number of studies using a retrospective cohort or prospective observational design.[9,13-16] The current level of evidence has some weaknesses and limitations. An association has been assessed using only a dichotomous approach (ie, exposure to inhibitors of gastric acidity: yes vs no). Moreover, the magnitude of association is uncertain, and the hypothesis of an association between inhibitors of gastric acidity and neonatal infections has not been tested using a prospective, randomized clinical trial design. Finally, it is not known whether any interaction exists between inhibitors of gastric acidity and concomitant prophylaxis with anti-infective medications.

In this study, we aimed to test the hypothesis that exposure to inhibitors of gastric acidity independently increases the risk of infections in preterm VLBW neonates. A second aim of this study was to explore the possible benefits of bovine lactoferrin (BLF) in preterm VLBW infants exposed to inhibitors of gastric acidity.

Methods

This is a secondary analysis of data obtained during a multicenter randomized controlled trial (RCT) (isrctn.org: ISRCTN53107700) performed in Italy and New Zealand from 2006 to 2010. The original study protocol, including structured criteria for inclusion/exclusion, enrollment, randomization, ethics, and institutional approvals, has been published previously.[17,18] In short, preterm VLBW neonates from 11 tertiary NICUs were enrolled before 72 hours of life and were randomly assigned to receive BLF alone (LF100; Dicofarm, Rome, Italy; 100 mg/day and 372 mg of fructo-oligosaccharides [FOS] per packet; group A1) or in combination with the probiotic *Lactobacillus rhamnosus* GG (LGG) (Dicoflor60; Dicofarm; 10^6 colony-forming units per day; group A2) or placebo (group B) from birth to day of life 30 (day of life 45 for those weighing <1000 g at birth). The drugs and placebo were administered orally, once daily. Neonates not feeding in the first 48 hours received the drug(s)/placebo by orogastric tube. The results from this RCT showed that BLF supplementation, either alone or in combination with LGG, reduces the risk of late-onset sepsis[18] and NEC[17] in VLBW infants compared with placebo.

In accordance with protocol, clinical and management data were collected prospectively for all enrolled infants until death or discharge. Systematic clinical surveillance for adverse events was performed through daily infant examination until 2 days after the end of treatment. Nutritional and feeding policies were stable during the study and consistent across centers, following common guidelines[19] and adherence to the study protocol.[18] Clinical surveillance for detection of sepsis was performed in all enrolled infants, with complete laboratory and microbiology evaluation in cases of suspected LOS.

In this secondary analysis, information regarding physicians' discretionary use, dosages, dosing schedules, and days of treatment of inhibitors of gastric acidity, as well as potential risk factors for infection, were reviewed from the study dataset, together with all data regarding fungal colonization and episodes of LOS.

The primary endpoint was the effect and magnitude of effect of inhibitors of gastric acidity exposure on the incidence of infections. We focused on the first episodes of LOS. Additional endpoints were to assess the effect of inhibitors of gastric acidity administration on fungal colonization and on NEC, the specific pathogens involved in the putative increased risk for sepsis attributable to inhibitors of gastric acidity, and whether oral supplementation of BLF (with or without the probiotic LGG) affects the occurrence of LOS and/or NEC in preterm VLBW neonates exposed to inhibitors of gastric acidity.

Inhibitors of gastric acidity were prescribed following common protocols and based on the clinical judgment of attending physicians, mainly for prevention of upper gastrointestinal bleeding (during medical treatment of patent ductus arteriosus) and management of oral feeding intolerance or gastroesophageal reflux in the enrolled infants. Dosages and schedules were the same for all participating centers, and followed current guidelines and recommendations. Ranitidine was administered at 0.5 mg/kg every 12 hours intravenously or 1-2 mg/kg every 8 hours orally. Cimetidine was administered at 2.5-5 mg/kg every 8-12 hours intravenously or orally. Omeprazole was dosed at 2-3 mg/kg/day. LOS was defined as an episode of infection occurring >72 hours after birth and before discharge, detected by clinical signs and symptoms, laboratory findings consistent with sepsis, and isolation of a causative organism from blood (drawn from peripheral sites), urine (collected by suprapubic puncture or bladder catheterization, with growth of >100 000 colony-forming units/mL [>10 000 for fungi]), or cerebrospinal or peritoneal fluid. Diagnostic criteria were based on the existing literature and guidelines from international consensus documents.[17,20-23]

Presumed sepsis (ie, clinical presentation consistent with sepsis without isolation of a microorganism) was not considered LOS, and thus was not analyzed in this study.

Systematic surveillance for detection of fungal colonization was performed through clinical and weekly surveillance cultures (at least 3 cultures per week from different periph-

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