Cohort Study of Probiotics in a North American Neonatal Intensive Care Unit

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Objective To determine whether routine probiotic administration to very preterm infants would reduce the incidence of necrotizing enterocolitis (NEC) without adverse consequences.

Study design Since the end of July 2011, we have administered a probiotic mixture to all admitted infants of <32 weeks' gestation. We give 0.5 g of a mixture of 4 bifidobacteria (*Bifidobacterium breve, bifidum, infantis,* and *longum*) and *Lactobacillus rhamnosus* GG (2×10^9 colony-forming units) per day, starting with the first feed, until the infant reaches 34 weeks. We compared complications among infants admitted during the first 17 months of routine use with those admitted during the previous 17 months.

Results Two hundred ninety-four infants received probiotics, and 317 infants formed the comparison group. Introduction of probiotics was associated with a reduction in NEC (from 9.8% to 5.4%, $P < .02$), a nonsignificant decrease in death (9.8% to 6.8%), and a significant reduction in the combined outcome of death or NEC (from 17% to 10.5%, $P < .05$). After adjustment for gestational age, intrauterine growth restriction, and sex, the improvements remained significant (OR for NEC, 0.51; 95% CI, 0.26-0.98; OR for death or NEC, 0.56; 95% CI, 0.33-0.93). There was no effect of probiotics on health care–associated infection.

Discussion A product that is readily available in North America, that has excellent quality control, and that contains strains similar to those that have been shown effective in randomized controlled trials substantially reduced the frequency of NEC in our neonatal intensive care unit. *(J Pediatr 2014;164:980-5)*.

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There are now >22 randomized controlled trials (RCTs) of probiotic preparations in preterm infants, enrolling >5000 infants.[1-15] Systematic reviews[16-18] of these trials have documented a major reduction in necrotizing enterocolitis (NEC) and a reduction in death with the routine use of probiotics in high-risk preterm infants. No significant adverse consequences of probiotic administration have been documented in the RCTs. Subgroup analyses demonstrate little difference in the effects of probiotics between those containing lactobacilli, those containing just *Bifidobacteria*, and those containing a mixture, although there are trends suggesting that a mixture of different organisms may be more effective than a single species.[19]

In Canada, probiotics sold as health-promoting agents are under the jurisdiction of the Natural Health Products Directorate, which has rigorous requirements for quality control and detailed labeling. To have a natural product number, the manufacturer must abide by Good Manufacturing Practice, in registered and inspected production facilities, have stringent quality control, and register the DNA of the organisms in a Health Canada database. No preparation of probiotic is licensed by Health Canada for the prevention of NEC. In 2011, faced with overwhelming evidence that probiotics could decrease NEC in preterm infants, and because there were no significant risks described in the extensive literature, we decided to introduce probiotics as routine care for the prevention of NEC. Before administering the probiotics, our laboratory personnel confirmed that they were able to grow the organisms in routine culture and perform generic identification confirming the presence of *Lactobacillus* and *Bifidobacteria*, but identification of the precise strain is not possible. In addition, a provincial service is available for further DNA analysis if necessary. We examined the clinical consequences of the introduction of probiotics in our neonatal intensive care unit (NICU) and hypothesized that serious cases of NEC would decrease following their introduction.

GI	Gastrointestinal
HCAI	Health care–associated infection
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
RCT	Randomized controlled trial
SGA	Small for gestational age

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The authors declare no conflicts of interest.

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Methods

We performed a prospective cohort study of infants receiving probiotics in our NICU. After the first 17 months of use, we compared the incidence of NEC and death with that during the final 17 months before the introduction of probiotics. We decided a priori that a period of 17 months before and after the introduction of probiotics should give a sample of about 300 eligible infants per group, given our usual frequency of admission of very preterm infants, and therefore 80% power to determine if there was a 60% reduction in NEC (from 10% to 4%, similar to the relative risk described in the systematic reviews) with a P value of .05.[20-22]

All infants admitted to the NICU at Sainte Justine University Health Center have their medical information recorded in the Canadian Neonatal Network Database. This information was used to identify infants for chart review. The Institutional Review Board of Sainte Justine approved both the anonymized prospective data collection and retrospective chart review. The study is reported following the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[23]

Since July 2011, all infants <32 weeks' gestation at birth were eligible to receive probiotics unless they had a gastrointestinal (GI) malformation. They received FloraBABY (Renew Life Canada, Oakville, Ontario, Canada) probiotic mixture; this was chosen because it has a Health Canada Natural Product Number and contains 4 *Bifidobacteria* (*Bifidobacterium breve, bifidum, infantis,* and *longum*) and *Lactobacillus rhamnosus* GG (2×10^9 colony-forming units per 0.5 g) mixed with 1 mL of water just before a milk feed once a day. Probiotics were started at the time of the first feed and continued until the infant reached 34 weeks' postmenstrual age. Infants who were receiving probiotics and developed NEC had probiotics discontinued for the period of being nil by mouth, and restarted afterward, in the hope of preventing recurrence of NEC. Probiotics were continued during sepsis or other acute illnesses unless the infant was placed nil by mouth.

Infants admitted to our NICU during the last 17 months before commencing probiotics, January 2010 to May 31, 2011, were included in the comparison group. We included all infants <32 weeks' gestation who were born at Sainte Justine or were transferred from another center before 3 days of age. Among data abstracted, we included gestation, sex, intrauterine growth restriction (ie, <10th percentile), having an umbilical catheter, being ventilated for at least the first 3 days of life, and completion of antenatal steroids.

In June and July 2011, administration of probiotics was not routine; 6 infants received probiotics, which were started after an episode of feeding intolerance or stage 1 or stage 2 NEC. Therefore, we did not include any data from infants born during June or July 2011. The protocol for routine administration was introduced in the last week of July 2011, and all infants <32 weeks' gestation admitted during the 17 months between August 1, 2011, and December 31, 2012, were included.

Outcome Variables

NEC was diagnosed on the basis of a combination of clinical signs and abdominal radiography and classified according to the modified Bell classification—stage 2 or 3 was considered definite NEC for the purposes of this study. The radiologists' reports were reviewed, and only those infants with a radiographic diagnosis of pneumatosis, portal venous air, or perforation were included as cases of NEC. The radiologists were unaware of the start of probiotic use in our NICU. Two infants had surgery despite not having other radiologic criteria for definite NEC; both had confirmatory pathology and are defined as being NEC. Mortality was defined as death before final discharge home. Infants presenting with typical clinical features of spontaneous intestinal perforation were not included as cases of NEC, unless the diagnosis was changed at the time of surgery.

Health care–associated infection (HCAI) was defined by a positive culture of a normally sterile body fluid (blood, cerebrospinal fluid, peritoneal fluid), occurring after 3 days of age. Length of stay was defined from date of birth until day of final discharge home. The day when probiotics were first actually received was recorded, as was the day they were stopped.

As a proxy for feeding tolerance, we recorded the day that intravenous nutrition was first stopped and the final day of receiving intravenous nutrition, including periods if it was restarted.

All infants born during the 2 study periods were included, including a few in the probiotic group who never received probiotics, either because of death or NEC occurring before the commencement of probiotics, or a few more mature infants (mostly of 31 weeks' gestation) who were not treated according to protocol, due to oversight.

Other Characteristics of Practice

About 1 year before the start of the first cohort, a new feeding protocol, designed to encourage the use of maternal breast milk and to rapidly advance feeds in preterm infants, was introduced in our NICU. There was no change in the protocol during the subsequent 4 years. Donor breast milk was not available during the entire study period; when breast milk was not available, infants received formula. The feeding protocol has guidelines for feeding in the presence of umbilical catheters and for feeding during treatment of a patent ductus arteriosus, which did not change during the study period.

Use of blood transfusions is not protocolized in our NICU, being prescribed according to perceived individual need by the attending staff, who did not change their approaches during this period.

Statistical Analyses

Data were analyzed initially by descriptive statistics. Initial comparison of the frequency of NEC and death and other categorical and continuous variables in the 2 groups used the Fisher exact test for proportional data and unpaired t tests

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