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## Oral Probiotics Reduce the Incidence and Severity of Necrotizing Enterocolitis in Very Low Birth Weight Infants

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**ABSTRACT.** *Objective.* We evaluated the efficacy of probiotics in reducing the incidence and severity of necrotizing enterocolitis (NEC) in very low birth weight (VLBW) infants.

*Patients and Methods.* A prospective, masked, randomized control trial was conducted to evaluate the beneficial effects of probiotics in reducing the incidence and severity of NEC among VLBW (<1500 g) infants. VLBW infants who started to fed enterally and survived beyond the seventh day after birth were eligible for the trial. They were randomized into 2 groups after parental informed consents were obtained. The infants in the study group were fed with Infloran (*Lactobacillus acidophilus* and *Bifidobacterium infantis*) with breast milk twice daily until discharged. Infants in the control group were fed with breast milk alone. The clinicians caring for the infants were blinded to the group assignment. The primary outcome was death or NEC ( $\geq$  stage 2).

*Results.* Three hundred sixty-seven infants were enrolled: 180 in the study group and 187 in the control group. The demographic and clinical variables were similar in both groups. The incidence of death or NEC ( $\geq$  stage 2) was significantly lower in the study group (9 of 180 vs 24 of 187). The incidence of NEC ( $\geq$  stage 2) was also significantly lower in the study when compared with the control group (2 of 180 vs 10 of 187). There were 6 cases of severe NEC (Bell stage 3) in the control group and none in the study group. None of the positive blood culture grew *Lactobacillus* or *Bifidobacterium* species.

*Conclusion.* Infloran as probiotics fed enterally with breast milk reduces the incidence and severity of NEC in

VLBW infants. *Pediatrics* 2005;115:1-4; *probiotics, necrotizing enterocolitis, sepsis, mortality, very low birth weight infants.*

ABBREVIATIONS. NEC, necrotizing enterocolitis; VLBW, very low birth weight.

Necrotizing enterocolitis (NEC) is a worldwide problem in very low birth weight (VLBW) infants, with highly variable incidence affecting 2.6% to 28% of these infants.<sup>1</sup> The precise pathogenesis of NEC is unknown but is widely considered as a multifactorial disease. Three major factors have been proposed: the presence of a pathogenic organism, the challenge of enteral feeding, and altered enteric mucosa integrity.<sup>2</sup> These factors may coalesce to produce bowel injury.<sup>2</sup> Although mortality rates among infants with NEC may have decreased as a result of improved supportive and surgical care, effective preventive strategies are lacking. Recently, various novel preventive strategies have been explored, including use of antenatal steroids,<sup>3</sup> breast milk feeding,<sup>4</sup> enhancement of platelet-activating factor acetyl hydrolase activity,<sup>5</sup> the use of platelet-activating factor receptor antagonists,<sup>6</sup> and probiotics.<sup>7-11</sup>

*Lactobacillus acidophilus*<sup>9</sup> and *Bifidobacterium infantis*<sup>10</sup> have been used as probiotics to reduce the incidence of NEC, but the dosage, duration, safety, and efficacy of probiotics remain controversial.<sup>9,10</sup>

Our hypothesis is that oral administration of probiotics in the form of Infloran (*L acidophilus* and *B infantis*) can reduce the incidence and severity of NEC in VLBW infants.

### PATIENTS AND METHODS

From July 1, 1999, to Dec 31, 2003, a prospective, masked, randomized control trial was conducted in the neonatal intensive care unit (NICU) of China Medical University Hospital, a level III neonatal center in the central part of Taiwan. The study was

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approved by our institutional review board. VLBW infants (birth weight <1500 g) who started to fed enterally and survived beyond the seventh day after birth were eligible for the trial. They were randomized into the study or control groups by a random-number table sequence after informed parental consents were obtained. The allocations were contained in opaque, sequentially numbered, sealed envelopes. The study group was fed with Infloran (*L acidophilus* [minimum of 1 004 356, obtained from the American Type Culture Collection in 1973] and *B infantis* [minimum of 1 015 697, obtained from the American Type Culture Collection in 1973]; Swiss Serum and Vaccine Institute, Berne, Switzerland): 125 mg/kg per dose twice daily with breast milk until discharged. The control group was fed with breast milk without the addition of probiotics. Infloran was stored in a refrigerator at a temperature between 4°C and 8°C and mixed with breast milk before feeding. Breast milk was either from the infant's own mother or from a breast milk bank. Infloran was added to the breast milk by personnel on the breast milk team who were not involved in the care of the infant and followed orders from the sealed envelope. Thus, the only personnel who knew of the infants' group assignments were the investigators and those on the breast milk team who were not involved in the care of the study infants.

Feeding was started when the infant had stable vital signs, active bowel sound without abdominal distension, no bile or blood from the nasogastric tube, and no indwelling umbilical artery or umbilical venous catheter for at least 24 hours. A strict feeding protocol was followed for all study infants. Depending on the birth weight and gestational age of the infant, a certain amount of breast milk was initiated after the infant tolerated 1 trial of distilled water. The amount of feeding was advanced slowly if tolerated, with no more than a 20 mL/kg per day increment per day. Feeding was stopped if there was any sign of feeding intolerance (defined as the presence of gastric aspirate in the amount that was more than half of the previous feeding, twice, with abdominal distension). Infants who weighed <1000 g received total parenteral nutrition until half of the calories were supplied by the oral route. The same attending physician was in charge of the care of the infants during their hospital stay. The residents who rotated through the NICU provided care following the established protocols of the unit. There were no modifications in management protocols, clinical practices, equipment, and infrastructure (such as nursing personnel) in the unit during the study period.

NEC is categorized by modified Bell's classification.<sup>12</sup> The diagnosis and classification of NEC was made by 2 independent senior attending neonatologists who did not know the group assignment of the infant. If they disagreed on the classification, a third attending neonatologist was asked to arbitrate. Demographic and clinical variables that are potential risk factors for NEC were prospectively abstracted from the medical records using the following definitions. A mother receiving 2 doses of betamethasone or dexamethasone given  $\geq 24$  hours before delivery was considered to have been on prenatal steroids. Infants with birth weight >2 SDs below the mean for gestational age were considered small for gestational age. Prolonged rupture of amniotic membrane was defined as rupture of the amniotic membrane >18 hours before delivery. Chorioamnionitis was defined as maternal fever, foul-smelling amniotic fluid, and left shift of the white blood cell differential count and was confirmed by the obstetrician. Asphyxia was defined by the following criteria: (1) an umbilical or scalp blood pH  $\leq 7.0$ , (2) an Apgar score of  $\leq 3$  at 5 minutes, (3) neurologic manifestation including hypotonia seizure or hypoxic-ischemia encephalopathy, and (4) multiple organs failure. Surfactant was used for respiratory distress syndrome within 2 hours after birth in cases of ventilated infants needing oxygen supplementation with a fractional inspired oxygen of  $\geq 0.40$  and showing radiologic changes typical of respiratory distress syndrome. Indomethacin was indicated in infants with patent ductus arteriosus showing left-to-right shunt by echocardiography. Sepsis was diagnosed for infants with clinical signs of sepsis occurring after randomization and was proven by positive blood culture. This event was not limited to being associated with death or NEC. Primary outcome was the incidence of death or NEC ( $\geq$  stage 2). Death was included as a primary outcome because it is a competing variable of NEC.

## Sample-Size Calculation and Statistics

Our historical data showed that the combined incidence of NEC or death was  $\sim 23\%$ . Setting the  $\alpha$  error  $< .05$  and  $\beta$  error  $< .2$  (2-tailed) and an absolute reduction of the incidence of NEC or death by 50%, the total number needed to verify our hypothesis was 338 (169 per arm of the study).

The  $\chi^2$  test was used to analyze the categorical data, along with Fisher's exact test when applicable. The Student's *t* test was used for continuous data. A logistic regression model was used to analyze the treatment effects on the primary and secondary outcome variables (death, NEC, and sepsis).

## RESULTS

There were 417 VLBW infants admitted to our NICU during the 4.5-year study period. Of these infants, 50 expired ( $n = 42$ ) or had NEC before 7 days after birth ( $n = 6$ ) or the family members declined consent for study ( $n = 2$ ). A total of 367 infants were enrolled in the trial: 180 in the study arm and 187 in the control arm. Fifty-six infants in the study group and 61 infants in the control group were fed with banked breast milk. The maternal clinical and infant's demographic and clinical characteristics did not differ between the 2 groups (Table 1). The infants' clinical characteristics also did not differ between the 2 groups (Table 2). None of the infants with asphyxia had NEC.

Table 3 shows the outcomes of the study by logistic regression analysis. The incidence of death or NEC was significantly lower in the probiotics group when compared with the control group (9 of 180 [5%] vs 24 of 187 [12.8%], respectively;  $P = .009$ ). The incidence of NEC was also lower in the probiotics when compared with the control group (2 of 180 [1.1%] vs 10 of 187 [5.3%], respectively;  $P = .04$ ). There were 6 cases of severe NEC (Bell stage 3) in the control group and none in the probiotics group ( $P = .03$  by bivariate analysis). The incidence of culture-proven sepsis was significantly lower in the study group ( $P = .03$ ). None of the positive blood cultures grew *Lactobacillus* or *Bifidobacterium* species. The incidence of NEC or sepsis was lower in the probiotic group (24 of 180 [13.3%] vs 46 of 187 [24.6%], respectively;  $P < .03$ ). The incidence of death, NEC, or

**TABLE 1.** Maternal Clinical and Infant's Demographic and Clinical Characteristics

| Characteristics                               | Study Group<br>(N = 180) | Control Group<br>(N = 187) |
|---|--------------------------|----------------------------|
| Prolonged rupture of amniotic membrane, n (%) | 53 (29.4)                | 43 (23.0)                  |
| Preeclampsia, n (%)                           | 26 (14.4)                | 24 (12.8)                  |
| Prenatal steroid, n (%)                       | 121 (67.2)               | 114 (61.0)                 |
| Cesarean section, n (%)                       | 104 (57.8)               | 100 (53.5)                 |
| Multipregnancy, n (%)                         | 34 (18.9)                | 33 (17.6)                  |
| Chorioamnionitis, n (%)                       | 9 (5.0)                  | 10 (5.3)                   |
| Male, n (%)                                   | 84 (46.7)                | 100 (53.5)                 |
| Small for gestational age, n (%)              | 42 (23.3)                | 41 (22.8)                  |
| Gestation, wk                                 | 28.5 $\pm$ 2.5*          | 28.2 $\pm$ 2.5*            |
| Birth weight, g                               | 1104 $\pm$ 242*          | 1071 $\pm$ 243*            |
| Apgar (5 min)                                 |                          |                            |
| <3  | 41                       | 44                         |
| 4-6   | 41                       | 49                         |
| >7  | 98                       | 94                         |
| Asphyxia, n (%)                               | 4 (2.2)                  | 6 (3.2)                    |
| pH  | 7.29 $\pm$ 1*            | 7.29 $\pm$ 11*             |

None of the differences are statistically significant ( $P > .05$ ).

\* Values are mean  $\pm$  SD.

**TABLE 2.** Clinical Variables in Study Infants

| Variables                                      | Study Group<br>(N = 180) | Control Group<br>(N = 187) |
|--|--------------------------|----------------------------|
| Age at enrollment,* d                          | 7.7 ± 2.0                | 7.9 ± 2.9                  |
| Nothing per ora,† d                            | 4.3 ± 3.5                | 4.4 ± 4.2                  |
| Total parenteral nutrition,‡ d                 | 14.7 ± 5.7               | 13.9 ± 5.0                 |
| Feeding amount at 14 d§                        | 79.7 ± 47.2              | 86.0 ± 49.3                |
| Feeding amount at 21 d*                        | 108.6 ± 51.3             | 114.1 ± 49.1               |
| Feeding amount at 28 d*                        | 120.0 ± 42.4             | 121.1 ± 45.4               |
| Use of surfactant, n (%)                       | 100 (55.6)               | 94 (50.2)                  |
| Umbilical artery catheter,* d                  | 0.7 ± 1.3                | 0.7 ± 1.4                  |
| Umbilical venous catheter,* d                  | 0.8 ± 1.4                | 0.8 ± 1.5                  |
| Intermittent mandatory ventilation,* d         | 9.6 ± 17.7               | 12.0 ± 21.0                |
| Pneumothorax, n (%)                            | 4 (2.2)                  | 3 (1.6)                    |
| O <sub>2</sub> * d                             | 33.9 ± 31.7              | 34.0 ± 34.6                |
| Use of dopamine, n (%)                         | 110 (61.1)               | 100 (53.5)                 |
| Dopamine,* d                                   | 3.5 ± 5.5                | 3.7 ± 6.1                  |
| Indomethacin, n (%)                            | 122 (67.8)               | 117 (62.6)                 |
| Age onset of NEC*                              | 19.5 ± 13.4              | 16.4 ± 11.7                |
| Intraventricular hemorrhage, grades 3–4, n (%) | 9 (5.0)                  | 14 (7.5)                   |
| NICU,* d                                       | 46.7 ± 27.1              | 46.5 ± 26.1                |

\* Values are mean ± SD. None of the differences are statistically significant ( $P > .05$ ).

† Days from birth to initiation of enteral feeding, mean ± SD.

‡ Duration of parenteral nutrition, mean ± SD.

§ mL/kg per day, mean ± SD.

**TABLE 3.** Outcome Variables After Oral Probiotics (Logistic Regression Analysis)

| Variables               | Study Group<br>(N = 180) | Control Group<br>(N = 187) | P Values |
|-------------------------|--------------------------|----------------------------|----------|
| Death                   | 7 (3.9)                  | 20 (10.7)                  | .009     |
| Death or NEC            | 9 (5)                    | 24 (12.8)                  | .009     |
| NEC grade 2 or 3        | 2 (1.1)                  | 10 (5.3)                   | .04      |
| Sepsis (culture proven) | 22 (12.2)                | 36 (19.3)                  | .03      |
| NEC or sepsis           | 24 (13.3)                | 46 (24.6)                  | .03      |
| Death or NEC or sepsis  | 31 (17.2)                | 60 (32.1)                  | .009     |

sepsis was significantly lower in the probiotic group (31 of 180 [17.2%] vs 60 of 187 [32.1%], respectively;  $P < .009$ ).

## DISCUSSION

Our study shows that Infloran reduces the incidence and severity of NEC in VLBW infants. We also found that the study group had a lower incidence of NEC and sepsis. According to our data, the number needed to treat to prevent 1 case of NEC is 27, and the number needed to treat to prevent 1 death due to NEC is 31.

Although many variables are associated with development of NEC, only prematurity<sup>13</sup> and low birth weight<sup>14</sup> have been consistently identified in case-controlled studies. Other factors that were associated with an increased risk of NEC were vaginal delivery, need for mechanical ventilator support, exposure to both glucocorticoids and indomethacin during the first week of life, absence of an umbilical arterial catheter, and low Apgar score at 5 minutes.<sup>14</sup> Because the current study was designed as a randomized, controlled trial, these risk factors were distributed randomly and showed no difference between the 2 study groups.

A major component of the proposed pathogenesis of NEC is the interaction of bacteria with the pre-

ture gut.<sup>15</sup> The fact that NEC does not occur in utero despite stress and fetal ingestion of 150 mL/kg per day of amniotic fluid that contains proteins, carbohydrates, fat, immunoglobulin, and electrolytes suggests that bacterial colonization is an important factor in the pathogenesis of this disease.<sup>16,17</sup> An animal model for NEC also demonstrated the need for bacterial colonization in the development of NEC.<sup>18,19</sup>

Intestinal microbiologic flora are an important factor in the host defense mechanism against bacterial infections. Lawrence et al<sup>20</sup> demonstrated that gut colonization with limited numbers and species of bacteria is delayed in a sterile environment. They speculated that lack of an aseptic environment in the NICU resulted in intestinal colonization with absorption of intact bacterial toxin, which may damage the immature ileum, resulting in the development of NEC. Hoy et al<sup>21</sup> and Millar et al<sup>22</sup> observed both a quantitative and qualitative change in the fecal flora before the onset of NEC. They observed a decline in the variety of species and shift to a predominance of Enterobacteriaceae before the onset of NEC. Gewolb et al<sup>23</sup> reported that *Bifidobacterium* and *Lactobacillus* are found in the stool of <5% of extremely low birth weight infants within the first month of life. These data suggest that low colonization of *Bifidobacterium* and *Lactobacillus* in VLBW infants may serve as a predisposing factor in microbial infection.

Potential mechanisms by which probiotics may protect high-risk infants from developing NEC include an increased barrier to translocation of bacteria and bacterial products across mucosa,<sup>24,25</sup> competitive exclusion of potential pathogens,<sup>26</sup> modification of host response to microbial products,<sup>27,28</sup> and enhancing enteral nutrition<sup>29</sup> that inhibits the growth of pathogens<sup>30,31</sup> such as *Klebsiella pneumoniae*,<sup>32</sup> *Escherichia coli*,<sup>33</sup> and *Candida albicans*.<sup>34</sup>

There is evidence from experimental data that supports the theory of microbial invasion as a contributing cause of NEC. This observation suggests that altering microbial flora by enteral feeding of probiotics may be beneficial. However, there is a paucity of clinical trials to confirm this hypothesis.<sup>9–11</sup>

Infloran has been used as probiotics to reduce the incidence of NEC by Hoyos.<sup>10</sup> In that study, one fourth of a tablet of Infloran was given to all infants admitted to the NICU. The results showed a significant reduction in the incidence of NEC and NEC associated death in the Infloran-treated infants when compared with historical controls. The study conclusion supported the notion of a randomized control trial to verify the efficacy of this strategy.

In a recent multicenter double-blind study, 585 infants of <33 weeks' gestational age or birth weight <1500 g who survived >2 weeks were randomized to receive either placebo or *Lactobacillus rhamnosus* GG once a day from the start of feeds to the time of discharge.<sup>9</sup> Outcome measures included the incidence of urinary tract infection, bacterial sepsis, and NEC. There were no significant differences between the probiotics and placebo groups in regards to any of the 3 outcome variables. However, the event rate was low in the control group for the 2 variables (NEC: 1.4%; sepsis: 3.4%), which needed a much

larger sample size to verify their hypothesis. There are other differences between that trial and ours. We used Infloran, a live probiotic cultured from the stool of neonates and containing *L acidophilus* and *B infantis*. Another difference is the age of study infants at enrollment: 1 week in our study and >2 weeks in their trial.

Our study showed that the study group has a lower incidence of NEC and sepsis. The mechanism for the efficacy of probiotics in reducing the incidence of sepsis in VLBW infants is probably similar to NEC<sup>35,36</sup> and possibly a result of increased colonization of desirable microflora such as *Streptococcus salivarius*.<sup>37</sup>

Although Wagner et al<sup>38</sup> suggested that safety issues of probiotics treatment need to be addressed in immunodeficient hosts such as neonates, we did not observe complications (such as *Lactobacillus* or *Bifidobacterium* sepsis) due to Infloran. However, our trial was not powered to evaluate safety in regards to the possible risk for *Lactobacillus* or *Bifidobacterium* sepsis.

We observed 6 infants with NEC before entry to the study and enteral feeding, 5 of whom were <1000 g. Probiotics alone could not eliminate the NEC, which further confirmed the theory that NEC is a multifactorial disease, of which intestinal colonization with unfavorable organisms is one.

## CONCLUSIONS

Oral Infloran administration in VLBW infants reduces the incidence and severity of NEC, and Infloran as probiotics is protective of NEC in VLBW infants.

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