Oral Probiotics Prevent Necrotizing Enterocolitis in Very Low Birth Weight Preterm Infants: A Multicenter, Randomized, Controlled Trial

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OBJECTIVE The goal was to investigate the efficacy of orally administered probiotics in preventing necrotizing enterocolitis for very low birth weight preterm infants.

METHODS A prospective, blinded, randomized, multicenter controlled trial was conducted at 7 NICUs in Taiwan, to evaluate the beneficial effects of probiotics in necrotizing enterocolitis among very low birth weight infants (birth weight: < 1500 g). Very low birth weight infants who survived to start enteral feeding were eligible and were assigned randomly to 2 groups after parental informed consent was obtained. Infants in the study group were given Bifidobacterium bifidum and Lactobacillus acidophilus, added to breast milk or mixed feeding (breast milk and formula), twice daily for 6 weeks. Infants in the control group were fed with breast milk or mixed feeding. The clinicians caring for the infants were blinded to the group assignment. The primary outcome measurement was death or necrotizing enterocolitis (Bell’s stage ≥2).

RESULTS Four hundred thirty-four infants were enrolled, 217 in the study group and 217 in the control group. The incidence of death or necrotizing enterocolitis (stage ≥2) was significantly lower in the study group (4 of 217 infants vs 20 of 217 infants). The incidence of necrotizing enterocolitis (stage ≥2) was lower in the study group, compared with the control group (4 of 217 infants vs 14 of 217 infants). No adverse effect, such as sepsis, flatulence, or diarrhea, was noted.

CONCLUSION Probiotics, in the form of Bifidobacterium and Lactobacillus, fed enterally to very low birth weight preterm infants for 6 weeks reduced the incidence of death or necrotizing enterocolitis. Pediatrics 2008;122:693–700

Necrotizing enterocolitis (NEC) is one of the most catastrophic gastrointestinal emergencies in very low birth weight (VLBW) preterm infants, affecting 7% to 14% of these infants. NEC is a leading cause of death and morbidity in NICUs, and the incidence of NEC has not changed in the past 20 years. Recent reports suggested the increasing occurrence of NEC and estimated up to 9000 cases of NEC in the United States every year, with a case fatality rate of 15% to 30%. The pathogenesis of NEC remains an enigma, but it is widely considered a multifactorial disease: prematurity, enteral feeding, intestinal hypoxia-ischemia, and bacterial colonization are considered major risk factors. Most likely, NEC is the clinical culmination of multiple risk factors that result in bowel injury through a final, common, inflammatory pathway.

It has been suggested that an inappropriate, accentuated, inflammatory response to colonizing pathogenic flora in the premature gastrointestinal tract plays a major role in the initiation of NEC. The inflammatory cascade promotes the spread of bacteria or toxin, resulting in ischemia, necrosis, and, in some cases, perforation. In vitro
evidence showed that pathogenic flora attach to the epithelial cells of preterm infants much more easily than to those of term infants, and studies indicated that commensal bacteria could inhibit or reduce inflammatory signaling in intestinal epithelia through inhibition of the NF-κB pathway. These data suggest that probiotics, by modifying the occurrence of these cascades of events, may play a major role in reducing the incidence of NEC.

Bin-Nun et al and we showed that orally administered probiotics reduce the incidence of NEC in VLBW preterm infants. Two meta-analyses arrived at the same conclusion; however, the limited number of clinical trials results in lack of definition of optimal strains, timing, dosage, and duration of probiotics administered to VLBW preterm infants, and these issues need to be evaluated in large trials. Furthermore, it has been speculated that the microbes of the developing intestinal tract of premature infants affect the maturation and functional playing a major role in reducing the incidence of NEC.

METHODOLOGY

We performed a pilot study from January 1, 2005, to March 31, 2005, to verify the viability of probiotic bacteria in the stool when Inforan (National Collection of Dairy Organisms, Reading, United Kingdom and Laboratorio, Farmaceutico, Mede, Italy) containing Lactobacillus acidophilus and Bifidobacterium bifidum was fed to VLBW preterm infants. Stool was collected for the first week of life from VLBW preterm infants (gestational age: <34 weeks; birth weight: <1500 g) who were fed Inforan in the NICU of China Medical University Hospital, after informed parental consent was obtained. Fecal samples were analyzed by using the methods reported by Lee et al; we confirmed that B bifidum and L acidophilus colonized the intestines of preterm infants fed Inforan.

From April 1, 2005, to May 30, 2007, a prospective, masked, randomized, controlled trial was conducted in 7 level III NICUs in Taiwan. The study protocol was approved by the institutional review board of each hospital. VLBW preterm infants (gestational age: <34 weeks; birth weight: <1500 g) who survived to feed enterally were eligible for the trial. They were assigned randomly to the study or control group by the principal investigator at each center after informed parental consent was obtained. Randomization was performed by using sequential numbers generated at the computer center of China Medical University Hospital and sent to the principal investigator at each center when an infant was eligible for enrollment. VLBW preterm infants who had severe asphyxia (stage III), fetal chromosomal anomalies, cyanotic congenital heart disease, congenital intestinal atresia, gastrochisis, or omphalocoele, those who were fed exclusively with formula, and those who were fasted for >3 weeks were excluded.

The study group was given Inforan L. acidophilus [10^9 colony-forming units, NCDO 1748; National Collection of Dairy Organisms] and B bifidum [10^9 colony-forming units, NCDO 1453; National Collection of Dairy Organisms, Reading, United Kingdom]; Laboratorio Farmaceutico, Italy) at 125 mg/kg per dose twice daily, through addition to breast milk or mixed feeding (breast milk and formula), for 6 weeks; the control group was fed breast milk or mixed feeding. Inforan was sent to each center and stored in a refrigerator at 2°C to 8°C. Inforan was added to breast milk (the infant’s own mother’s milk) or formula by the breast milk team before feeding. Both breast milk and formula for the study and control groups were prepared by the breast milk team, who did not know the colony counts of probiotics and were not involved in the care of the infants. The team members followed the orders from a sealed envelope. Therefore, the only personnel who knew of the infants’ group assignments were the investigators at each center and those on the breast milk team, who were not involved in the care of the study infants.

The indications for feeding and a strict feeding protocol were followed for all study infants, as described in a previous study. Depending on the birth weight and gestational age, a certain amount of breast milk was initiated after the infant tolerated 1 trial of distilled water. On the first day, 1 mL/kg distilled water was given twice, followed by breast milk. The amount of feeding was increased slowly if tolerated, with increments of no more than 20 mL/kg per day per feeding. An oral intake of 100 mL/kg per day was defined as complete enteral feeding. Feeding was stopped if there was any sign of feeding intolerance, defined as the presence of gastric aspirate in an amount that was more than one half of the previous feeding, twice, with abdominal distension. Infants who weighed <1000 g received total parenteral nutrition until one half of their energy was supplied through 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 by following established protocols in the unit. Definitions of prenatal steroid use, small for gestational age, prolonged rupture of amniotic membranes, chorioamnionitis, asphyxia, respiratory distress syndrome, patent ductus arteriosus, IVH, PVL, and sepsis and indications for surfactant and indomethacin were as described in our previous study. The management protocols, clinical practices, equipment, infrastructure, and key personnel in each unit were unchanged during the study period. A consensus was obtained among the 7 participating centers regarding the definition and prospective collection of demographic and clinical outcome variables. The data collected by each center were trans-
were 217 infants in the study arm and 217 in the control group. Two infants in the study group and 1 in the control group dropped out of the program because of parental wishes. A total of 443 infants were enrolled in the trial; 3 infants or family members declined consent for the study (n = 3). The mothers’ clinical and infants’ demographic and clinical characteristics did not differ between the 2 groups, except for lower birth weight and first arterial blood pH values in the study group (Table 1). The infants’ clinical variables also did not differ between the 2 groups, except for more frequent use of surfactant replacement therapy in the study group (Table 2).

Table 3 shows the primary outcomes of the study. The incidence of death or stage ≥2 NEC (4 of 217 infants vs 20 of 217 infants; P = .002) was significantly lower in the study group, compared with the control group. Two infants in the study group and 9 infants in the control group developed stage 2 NEC; 2 infants in the study group and 5 infants in the control group developed stage 3 NEC. Four and 14 infants developed stage ≥2 NEC in the study and control groups, respectively (P < .02). There was no difference between the study group and control group in the incidence of death attributable to NEC.

### TABLE 1 Perinatal Variables for Study Infants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study (N = 217)</th>
<th>Control (N = 217)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROM, n (%)</td>
<td>59 (21.2)</td>
<td>64 (29.2)</td>
<td>.55</td>
</tr>
<tr>
<td>Preeclampsia, n (%)</td>
<td>37 (17.0)</td>
<td>37 (17.2)</td>
<td>.97</td>
</tr>
<tr>
<td>Prenatal steroid treatment, n (%)</td>
<td>107 (49.3)</td>
<td>96 (44.4)</td>
<td>.33</td>
</tr>
<tr>
<td>Ammonitosis, n (%)</td>
<td>16 (7.4)</td>
<td>14 (6.5)</td>
<td>.72</td>
</tr>
<tr>
<td>Cesarean section, n (%)</td>
<td>149 (69.6)</td>
<td>136 (63.3)</td>
<td>.16</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>122 (56.2)</td>
<td>115 (53)</td>
<td>.50</td>
</tr>
<tr>
<td>SGAG, n (%)</td>
<td>47 (21.7)</td>
<td>46 (21.2)</td>
<td>.91</td>
</tr>
<tr>
<td>Apgar score of &lt;6 at 5 min, n (%)</td>
<td>61 (28.5)</td>
<td>50 (23.5)</td>
<td>.24</td>
</tr>
<tr>
<td>Asphyxia, n (%)</td>
<td>8 (3.7)</td>
<td>5 (2.3)</td>
<td>.58</td>
</tr>
<tr>
<td>Birth weight, mean ± SD, g</td>
<td>1028.9 ± 246.0</td>
<td>1077.3 ± 214.4</td>
<td>.03</td>
</tr>
<tr>
<td>First arterial pH, mean ± SD</td>
<td>7.26 ± 0.13</td>
<td>7.29 ± 0.11</td>
<td>.01</td>
</tr>
</tbody>
</table>

Prom indicates prolonged rupture of membrane; SGAG, small gestational age.

* By t test or χ² test.

** By Fisher’s exact test.

Figure 1 shows the flow of study subjects through the phases of the study. There were 580 VLBW preterm infants admitted to the 7 NICUs during the study period. One hundred thirty-seven infants were excluded; either they died (n = 98), they met the exclusion criteria (n = 14), or family members declined consent for the study (n = 25). A total of 443 infants were enrolled in the trial: 3 infants in the study group and 1 in the control group dropped out of the program because of parental wishes to withdraw the infants from the trial. Two infants in the study group and 3 in the control group underwent spontaneous intestinal perforation and were excluded. There were 217 infants in the study arm and 217 in the control arm. The mothers’ clinical and infants’ demographic and clinical characteristics did not differ between the 2 groups, except for lower birth weight and first arterial blood pH values in the study group (Table 1). The infants’ clinical variables also did not differ between the 2 groups, except for more frequent use of surfactant replacement therapy in the study group (Table 2).

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NEC, stage 3

Death or NEC

Death not attributable to NEC

Pneumothorax

Antibiotics at 2 wk, n (%) 136 (62.67) 115 (53.24) .05

Antibiotics at 4 wk, n (%) 99 (46.26) 100 (46.95) .89

Antibiotics at 6 wk, n (%) 65 (30.52) 64 (30.62) .36

Age at enrollment, mean ± SD, d 4.5 ± 3.0 4.3 ± 3.2 .07

UAC use, mean ± SD, d 3.5 ± 1.5 3.6 ± 1.1 .73

UVC use, mean ± SD, d 4.4 ± 1.8 4.1 ± 1.6 .31

IMV, mean ± SD, d 16.6 ± 24.2 13.8 ± 24.5 .22

Dopamine treatment, mean ± SD, d 5.0 ± 4.3 6.1 ± 8.2 .20

Age at onset of NEC, mean ± SD, d 30.8 ± 14.9 22.7 ± 16.6 .40

NICU stay, mean ± SD, d 46.4 ± 24.2 43.3 ± 21.0 .16

EBM feeding, n (%) 150 (69.12) 134 (61.75) .11

Mixed feeding, mean ± SD, d 43.6 ± 14.7 44.0 ± 20.3 .83

UAC indicates umbilical artery catheter; UVC, umbilical venous catheter; IMV, intermittent mandatory ventilation; EBM, exclusive breast milk.

a By t test or χ² test.

b By Fisher’s exact test.

Table 2 Clinical Variables for Study Infants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study (N = 217)</th>
<th>Control (N = 217)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of surfactant, n (%)</td>
<td>136 (62.67)</td>
<td>115 (53.24)</td>
<td>0.05</td>
</tr>
<tr>
<td>Pneumothorax, n (%)</td>
<td>4 (1.84)</td>
<td>3 (1.4)</td>
<td>1.00b</td>
</tr>
<tr>
<td>Indomethacin dose, mean ± SD, mg/kg</td>
<td>2.8 ± 1.8</td>
<td>2.8 ± 2.1</td>
<td>0.89</td>
</tr>
<tr>
<td>Antibiotics at 2 wk, n (%)</td>
<td>99 (46.26)</td>
<td>100 (46.95)</td>
<td>0.89</td>
</tr>
<tr>
<td>Antibiotics at 4 wk, n (%)</td>
<td>65 (30.52)</td>
<td>64 (30.62)</td>
<td>0.36</td>
</tr>
<tr>
<td>Antibiotics at 6 wk, n (%)</td>
<td>41 (19.43)</td>
<td>39 (19.4)</td>
<td>0.88</td>
</tr>
<tr>
<td>Age at enrollment, mean ± SD, d</td>
<td>4.5 ± 3.0</td>
<td>4.3 ± 3.2</td>
<td>0.07</td>
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<tr>
<td>UAC use, mean ± SD, d</td>
<td>3.5 ± 1.5</td>
<td>3.6 ± 1.1</td>
<td>0.73</td>
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<tr>
<td>UVC use, mean ± SD, d</td>
<td>4.4 ± 1.8</td>
<td>4.1 ± 1.6</td>
<td>0.31</td>
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<tr>
<td>IMV, mean ± SD, d</td>
<td>16.6 ± 24.2</td>
<td>13.8 ± 24.5</td>
<td>0.22</td>
</tr>
<tr>
<td>Dopamine treatment, mean ± SD, d</td>
<td>5.0 ± 4.3</td>
<td>6.1 ± 8.2</td>
<td>0.20</td>
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<tr>
<td>Age at onset of NEC, mean ± SD, d</td>
<td>30.8 ± 14.9</td>
<td>22.7 ± 16.6</td>
<td>0.40</td>
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<tr>
<td>NICU stay, mean ± SD, d</td>
<td>46.4 ± 24.2</td>
<td>43.3 ± 21.0</td>
<td>0.16</td>
</tr>
<tr>
<td>EBM feeding, n (%)</td>
<td>150 (69.12)</td>
<td>134 (61.75)</td>
<td>0.11</td>
</tr>
<tr>
<td>Mixed feeding, mean ± SD, d</td>
<td>43.6 ± 14.7</td>
<td>44.0 ± 20.3</td>
<td>0.83</td>
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</table>

Table 3 Primary Outcomes of Study

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n</th>
<th>Study (N = 217)</th>
<th>Control (N = 217)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or NEC</td>
<td>4</td>
<td>20</td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td>NEC, stage 2</td>
<td>2</td>
<td>9</td>
<td>.27</td>
<td></td>
</tr>
<tr>
<td>NEC, stage 3</td>
<td>2</td>
<td>5</td>
<td>.13</td>
<td></td>
</tr>
<tr>
<td>NEC, stage ≥2</td>
<td>4</td>
<td>14</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>Death attributable to NEC</td>
<td>2</td>
<td>3</td>
<td>.98</td>
<td></td>
</tr>
<tr>
<td>Death not attributable to NEC</td>
<td>0</td>
<td>6</td>
<td>.04</td>
<td></td>
</tr>
</tbody>
</table>

a By t test or χ² test.

Table 4 summarizes the findings of different weight groups. The incidence of NEC was significantly lower in infants weighing <750 g and 751–1000 g (p = 0.02) and 1001–1500 g (p = 0.02), but not in infants weighing 751–1000 g. Incidence of NEC was significantly lower in infants weighing 1001–1500 g (p = 0.02), but not in infants weighing >1000 g. Occurrence of sepsis was most often in the infants weighing <1000 g. The incidence of Gram-positive and Gram-negative sepsis did not differ between study and control groups for infants in the different weight groups.

Table 4 shows that the age of attainment of full feeding and weight gain at various ages were similar between the 2 groups.

**DISCUSSION**

This is the first multicenter, randomized, controlled trial that showed efficacy of probiotics containing *B. bifidum* and *L. acidophilus* in reducing the incidence of NEC among VLBW preterm infants. We also found that the study group had a lower incidence of death or NEC. According to our data, the number needed to treat to prevent 1 case of NEC was 20 patients, and the number needed to treat to prevent 1 death or case of NEC was 14 patients.

Many variables have been suggested to be associated with the development of NEC; however, only prematurity and low birth weight have been consistently identified in case-control studies. The current study was designed as a multicenter, randomized, controlled trial. During the randomization process, we neglected to stratify according to birth weight, which resulted in an imbalance of patient assignment to the study and control groups, with the birth weight being lower in the former group. The lower birth weight also accounts for the greater acuity of the infants’ illness, as evidenced by lower first arterial pH and more frequent use of surfactant therapy. The difference in birth weight was because there were 33 infants in the study group but only 18 infants in the control group who weighed >750 g. However, in the study group, there was lower incidence of death or NEC in different weight groups; incidence NEC tended to be lower in each weight group and no infants died with NEC. We addressed this methodologic deficiency by performing posthoc, multivariate, logistic regression analysis, entering potential risk factors that could bias the results (eg, birth weight and first arterial pH). Additional support for the validity of our data was the demonstration that the incidence of the primary study outcome (death or NEC) remained lower in the
probiotic-treated group. Because center variation can play an important role in outcome, we included center outcomes in the model.

Because of the methodologic misstep that caused uneven distribution of the weight groups and resulted in fewer infants weighing <750 g in the control group, it is difficult to interpret the results for infants weighing <750 g because of type II error. In the study group, however, there were significantly lower incidences of death or NEC in different weight groups; the incidence of NEC tended to be lower in each weight group, and no infants died as a result of causes other than NEC. Additional research with an adequate number of weight-stratified infants is urgently needed to help define the beneficial effects of probiotics in each group.

The ability of bacteria to cross epithelial cell layers is thought to be a crucial first step in the cascade of events leading to the development of NEC.28,29 Bacterial interactions with the premature gut might play a major role in the proposed pathogenesis of NEC; many studies suggest a strong relationship between delay and low colonization of commensal flora and proliferation of pathogenic flora in the immature gut, predisposing preterm infants to develop NEC.28-32 Using animal models, Caplan et al33 and Butel et al34 showed that bifidobacterial supplementation in rat pup and quail models resulted in intestinal colonization and subsequent reduction in NEC-like lesions. Our findings of a beneficial effect of oral probiotic supplementation may be based on this mechanism. Bifidobacteria and lactobacilli have been shown to inhibit intestinal colonization of pathogenic microorganisms, to produce protective nutrients, and to prevent translocation of other bacteria.35 These characteristics support the use of *Bifidobacterium* and *Lactobacillus* as appropriate species of probiotics for the prevention of NEC.

The probiotics we used in the current study were different from those in our previous study, because the supplier of the probiotics altered the formula by changing *Bifidobacterium infantis* (used in our previous trial) to *B bifidum* (used in current study). In the study by Bin-Nun et al,15 the probiotics contained *B infantis, Streptococcus thermophilus,* and *B bifidum.* Molecular studies have indicated that *Bifidobacterium* spp in the intestinal tract can range from 60% to 90% of the total fecal microbiota in breastfed infants, and lactic acid-producing bacteria may account for <1% of the total microbiota, indicating the significant dominance of *Bifidobacterium.*36 Studies also indicated that *B bifidum, Bifidobacterium longum,* and *Bifidobacterium breve* are the most common strains in healthy breastfeedings.37 A recent study showed that *B bifidum* is a promising candidate for probiotic intervention in inflammatory disorders of the gastrointestinal tract.39 On the basis of these clinical trials and in vitro studies, it is reasonable to speculate that probiotics that contain *Bifidobacterium* might be most appropriate for the prevention of NEC.

Human milk feeding has been shown to reduce the incidence of NEC but cannot eradicate NEC, as in this study. Three of 4 infants in the study group and 6 of 14 infants in the control group were receiving exclusive breast milk feeding but still developed NEC. It has been

<table>
<thead>
<tr>
<th>Outcome Variables at Each Center</th>
<th>( n )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or NEC</td>
<td>( A(N = 63) )</td>
</tr>
<tr>
<td>NEC, stage ( \geq 2 )</td>
<td>4</td>
</tr>
<tr>
<td>Death not attributable to NEC</td>
<td>1</td>
</tr>
<tr>
<td>Death attributable to NEC</td>
<td>0</td>
</tr>
<tr>
<td>Sepsis</td>
<td>9</td>
</tr>
<tr>
<td>CLD</td>
<td>18</td>
</tr>
<tr>
<td>PVL</td>
<td>3</td>
</tr>
<tr>
<td>IVH, grade ( \geq 3 )</td>
<td>2</td>
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</table>

A to G represent the neonatal centers.
shown that human milk feeding may not eliminate NEC because of interleukin 10 deficiency. Both *Bifidobacterium* and *Lactobacillus* has been shown to induce IL10 production. Breastfeeding promotes a strong bifidobacterial presence in the infant gut by providing oligosaccharides that act as favorable substrates for bifidobacteria. Oral administration of specific strains of *Lactobacillus* and human milk may have synergistic effects with bifidobacteria and lactobacilli to inhibit the inflammatory response in NEC. In the current study and as in most NICUs, a large majority of infants were fed human milk; therefore, it was difficult to demonstrate potential synergistic effects of probiotics and human milk.

Our previous study\(^6\) and other studies\(^4,45\) showed that probiotics may reduce the incidence of sepsis; however, meta-analysis did not confirm this association.\(^17,18\) The number of patients accumulated in our previous study, and occurrences of sepsis even seemed more frequent in the study group. Our previous study did not examine sepsis in detail. We analyzed the frequency of sepsis according to Gram-positive, Gram-negative, and fungal infections and found that the pathogens were most often related to catheter-related infections in both groups. Theoretically, changing the intestinal ecosystem could not prevent Gram-positive sepsis. The incidence of Gram-negative sepsis was higher in the study group, but no difference was observed in either univariate analysis or logistic regression analysis with risk factors. It is well known that risk factors for late-onset sepsis include young gestational age, use of a central line, total parenteral nutrition, and prolonged use of mechanical ventilation, among others.\(^4\) We speculate that probiotics would not prevent late-onset sepsis because of the complexity of this disorder. Probiotics alone could not overcome the invasive procedures inducing infection. The same speculation can be made regarding the nonsignificant effects on CLD, IVH, and PVL. The primary effect of orally administered probiotics is in the gastrointestinal tract. It is not surprising to see the lack of beneficial effects on other organs, such as the lung and central nervous system.

A few case reports have raised concerns regarding infections with probiotic microorganisms in patients who are immunocompromised or have underlying medical conditions predisposing them to infection.\(^47,48\) However, it was noted by Presterl et al\(^46\) that some *Lactobacillus* strains can be found in the intestinal microbiota of healthy humans, and the source of infection in those cases cannot be conclusively proven.\(^49\) In a review of the literature, there were no reports of bifidobacterial sepsis related to probiotic use; this is in keeping with animal studies that suggest low pathogenicity.\(^50\) Although Kunz et al\(^35\) described 2 premature infants who developed *Lactobacillus* bacteremia while taking *Lactobacillus* rhamnosus GG (LGG) supplements, both of those preterm infants had short-gut syndrome; other authors and we did not observe sepsis attributable to probiotic organisms during the studies.\(^15-18\) The number of patients accumulated from all clinical trials may yield enough power to state that treatment is relatively safe, comparing the possible sepsis attributable to probiotics (0 of 940 patients; sum of all clinical trials including ours)\(^17,18\) with the higher incidence (7%–14%) and disastrous effects of NEC for VLBW infants.

The incidence of NEC or death was lower than the expected effect size we used in the sample size calculation. This may be partly a result of improvements in the quality of care for VLBW infants in Taiwan. It may also
be attributable to the fact that the sickest infants were not enrolled in the study, because they either died before feeding or were not fed before 3 weeks of age. We conclude that probiotics containing \textit{B. bifidum} and \textit{L. acidophilus}, administered orally for 6 weeks, reduce the incidence of death or NEC for VLBW preterm infants.

**ACKNOWLEDGMENTS**

This study was supported by the National Science Council of Taiwan (grant NSC 94-2314-B-039-007) and was approved by the institutional review board of China Medical University Hospital (proposal DMR94-IRB-14).

We thank our wonderful team members; this work would not have been possible without their active cooperation. We express sincere gratitude to Prof Wen-Miin Liang and Li-Na Liao in the Biostatistics Center, China Medical University, for their outstanding work on the statistical analyses. We also acknowledge the editorial assistance of Dr William Oh in the preparation of the manuscript.

**REFERENCES**


**TRYING TO SAVE BY INCREASING DOCTORS’ FEES**

“Cutting health costs by paying doctors more? That is the premise of experiments underway by federal and state government agencies and many insurers around the country. The idea is that by paying family physicians, internists and pediatricians to devote more time and attention to their patients, insurers and patients can save thousands of dollars downstream on unnecessary tests, visits to expensive specialists and avoidable trips to the hospital. Nationally, Medicare and commercial insurers pay an average of only about $60 a visit to the office of a primary-care doctor and rarely if ever pay for telephone or e-mail consultations. Many health policy experts say the payments are not enough to let the doctors spend more than a few minutes with each patient. Richard Baron is one of more than 100 physicians in metropolitan Philadelphia taking part in the experiment, which is being conducted jointly by some of the region’s largest insurers. Dr Baron still gets a fee of only about $64 for each office visit. But his five-doctor group will also receive $200 000 to $300 000 this year beyond their regular fees to keep better track of their 8400 patients. ‘We are trying to do more e-mail care and telephone care, which we haven’t been paid for in the past,’ Dr Baron said. Insurers are conducting similar pilot projects in at least a half-dozen states, in experiments involving thousands of doctors and nearly two million patients.’ Such features add up to a model of primary care that proponents refer to as providing people with a ‘medical home’—a base where doctors, staff and patients pull together as one big health-care family. Or at least that is the ideal. ‘It’s the latest new, new thing—testing whether medical homes can be a vehicle for pulling America upwards from the grossly inefficient swamp in which our health system is currently mired,’ said Dr Arnold Milstein, a senior consultant at Mercer who is also a member of the Medicare Payment Advisory Commission, an independent Congressional agency.


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Pediatrics 2008;122:693-700
DOI: 10.1542/peds.2007-3007

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