Long-term consumption of infant formulas containing live probiotic bacteria: tolerance and safety

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ABSTRACT

Background: Nonpathogenic live bacteria are consumed as food by many children, particularly in the form of yogurt. The tolerance and safety of long-term consumption of specific types and strains of probiotic bacteria are not well documented.

Objective: The goal was to evaluate tolerance to formulas containing 2 levels of probiotic supplementation and effects on growth, general clinical status, and intestinal health in free-living healthy infants.

Design: This was a prospective, double-blind, randomized, placebo-controlled study of healthy infants aged 3–24 mo. Infants were assigned to receive a standard milk-based formula containing 1 × 10^7 colony-forming units (CFU)/g each of Bifidobacterium lactis and Streptococcus thermophilus, formula containing 1 × 10^6 CFU/g each of B. lactis and S. thermophilus, or unsupplemented formula. Clinical outcomes included formula intake, gastrointestinal tolerance, anthropometric measures, daycare attendance, and history of illness.

Results: One hundred eighteen infants aged (x ± SD) 7.0 ± 2.9 mo at enrollment consumed formula for 210 ± 127 d. There were no significant differences in age, sex, formula consumption, or length of study between groups. The supplemented formulas were well accepted and were associated with a lower frequency of reported colic or irritability (P < 0.001) and a lower frequency of antibiotic use (P < 0.001) than was the unsupplemented formula. There were no significant differences between groups in growth, health care attention seeking, daycare absenteeism, or other health variables.

Conclusion: Long-term consumption of formulas supplemented with B. lactis and S. thermophilus was well tolerated and safe and resulted in adequate growth, reduced reporting of colic or irritability, and a lower frequency of antibiotic use. Am J Clin Nutr 2004;79:261–7.

KEY WORDS Probiotics, infant formula, growth, tolerance, infants

INTRODUCTION

The deliberate consumption of nonpathogenic live bacteria, usually in the form of fermented dairy products, has been practiced for centuries. More recently, specific types of bacteria have been increasingly included in human diets for their potential health benefits; these bacteria are referred to in the literature as probiotic agents (1). Numerous studies have documented the beneficial effects of live microbial agents given orally for diarrheal disease, Clostridium difficile colitis, and antibiotic-associated diarrhea and the possible effects on allergic disease (2–5). Several of these agents are regularly consumed by children and in some parts of the world by infants, usually in the form of yogurt or other cultured milk products. Although many of these agents have been shown in a large number of studies to be innocuous, most of these studies were short-term trials, many of which were uncontrolled and a good number of which were conducted in adult populations. Additionally, some instances of bacteremia and adverse effects have been reported in high-risk populations (6, 7).

There are few reports or controlled studies in the literature specifically, prospectively, and carefully documenting the effects of feeding large amounts of live active bacteria to infants for any extended period of time. Thus, adequate documentation of safety with prolonged use in infants is mandatory if recommendations for use are to be made in this population. The purpose of the present study was therefore to prospectively follow a group of free-living healthy infants receiving formula containing Bifidobacterium lactis (strain Bb 12) and Streptococcus thermophilus at 2 levels of supplementation, to identify any adverse effects, and to examine effects on growth, general clinical status, and intestinal health.

SUBJECTS AND METHODS

Subjects

Over a period of 18 mo, 131 healthy infants were recruited from 27 daycare centers from the metropolitan area of Baltimore. All parents of children aged between 3 and 24 mo attending these centers were approached for participation. Children were selected on the basis of their parents’ willingness to participate in the study. The only exclusion criteria were breastfeeding ≥3 times/d, a history of allergy to standard formula, or a history of chronic diarrhea or malabsorptive syndrome.

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2 Supported by a research grant from Nestlé USA. All study formulas were provided by Nestlé USA, Glendale, CA.
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Study design

The recruited subjects were randomly assigned according to a variable-size block scheme to receive 1 of 3 formulas ad libitum: 1) a standard formula supplemented with _B. lactis_ (strain Bb 12) and _S. thermophilus_ at a concentration of \( \approx 1 \times 10^7 \) colony-forming units (CFU)/g [high-supplement (HS) formula]; 2) the same formula supplemented at a concentration of \( 1 \times 10^6 \) CFU/g [low-supplement (LS) formula]; or 3) the same formula without any supplementation (placebo formula). Subjects remained in the study as long as they maintained an intake of \( \geq 240 \text{ mL (8 oz)} \) study formula/d. Subjects were not considered to meet the inclusion criteria once their intake fell below the minimum of 240 mL (8 oz)/d or they no longer attended a participating daycare center.

Data were collected weekly throughout the study through phone calls to the parents and visits to the daycare centers. Two study questionnaires were developed and administered to the parents and the caregivers in a standardized fashion by 3 trained research data collectors. The weekly phone call questionnaire administered to the parents was used to collect the following information:

1) information on the general health status of the infant, eg, occurrence of any illness, health care visits for sickness, missed daycare days for illness, and antibiotic use;
2) gastrointestinal signs and related symptoms, eg, loose stools, discomfort passing bowel movements, vomiting and regurgitation, and colic or irritability;
3) dietary information, eg, any breastfeeding (to ensure compliance with enrollment criteria) and intake of any other formula or liquid foods; and
4) data used to monitor compliance by the parents and caregivers in preparing and feeding the formula, eg, the type of study formula being offered (formulas were identified by color of label), amount of formula consumed by the infant, and changes in amounts being offered.

At the daycare centers, data on attendance, anthropometric variables, and study formula intake at the daycare center were collected weekly by research associates using standardized protocols. Monthly weight and length measurements were made according to standardized techniques by using an infant stadiometer (length board) and infant digital scale. All data (weekly phone interview, daycare visits, and anthropometric variables) were collected throughout each child’s participation in the study.

Study formulas

The 3 study formulas were all standard milk-based powder products (commercially available) that when prepared in accordance with the label instructions contained 2.80 kJ/mL and 2.6 g protein, 4.1 g fat, and 13.2 g carbohydrates/418 kJ (100 kcal). Formulas were supplied by Nestlé USA, Glendale, CA. All of the formula components were standard ingredients used for feeding healthy children, and the formula composition complied with American Academy of Pediatrics and Food and Drug Administration standards.

The _B. lactis_ (strain Bb 12) and _S. thermophilus_ used in the supplemented formulas were obtained from and certified by Chris Hansen Laboratories, Copenhagen. Taxonomy of the organisms was confirmed by using standard microbiological techniques. Throughout the study, a monthly quantitative bacterial count of the formula was done by using standard MRS, M17, and Garché’s media to monitor bacterial stability counts and to calculate bacterial intake by the subjects over their study participation.

Ethics

The study was reviewed and approved by the Investigational Review Board of the Johns Hopkins Medical Institutions. Written informed consent was obtained from all subjects’ parents before participation. Subjects received the study formula free of charge delivered to the daycare centers. Each child’s pediatrician was informed in writing of the child’s participation in the study. A toll-free phone number was available to the participants at all times for them to ask questions and report any perceived problems or concerns.

Statistical analysis

Data analysis was conducted by using the STATA statistical package (version 5.0; Stata Corp, College Station, TX). Analysis of categorical outcomes and formula groups was based on chi-square (Pearson) or Student’s _t_ tests, as appropriate. To account for potential autocorrelation of longitudinal data (eg, frequency of reporting of clinical outcomes), generalized estimating equations models were used for all longitudinal variables, including growth points (weight, height, and weight/height) and length of study participation. For each child, values for weight, length, and weight-for-length were converted into percentiles and _t_ scores for age and sex by using reference data from the National Center for Health Statistics (8) and were analyzed as such. The study was designed to follow subjects from the time of initiation of consumption until they no longer met the study inclusion criteria. Subjects were terminated from the study once they stopped meeting the inclusion criteria, including lack of exposure to the daycare environment and cessation of formula intake, usually as a result of the natural weaning process. All data from all subjects meeting the protocol criteria were included in the analysis. The only subjects who were excluded from the analysis were those who participated for \( <14 \text{ d} \) or consistently consumed \( <240 \text{ mL (8 oz)} \) formula/d.

RESULTS

Study population

Of 131 infants recruited, 11 (5 in the HS group, 2 in the LS group, and 4 in the placebo group) received formula for \( <14 \text{ d} \) and were excluded from further analyses; 2 infants (in the LS group) were excluded for taking \( <240 \text{ mL (8 oz)} \) formula/d for 15 or 18 d, respectively. The remaining 118 infants constituted the study population. Of the 11 infants who consumed formula for \( <14 \text{ d} \), the parents of 2 changed their minds about participation, 1 infant left the daycare center, the parents of 3 perceived that their child refused to take the formula or “did not like it,” and 5 infants had an intercurrent illness the week they started, and their parents withdrew their participation. Of these 5 infants with an intercurrent illness or complaint, 4 had vomiting and diarrhea (1 in the placebo group and 3 in the HS group) and 1 (in the HS group) had otitis media. The age range...
of the study population at the time of enrollment was 2.7–12.9 mo (± SD: 7.0 ± 2.9 mo; Table 1). Fifty-eight of the infants were male, and 60 were female.

Thirty-nine subjects were randomly assigned to the HS formula, 39 to the LS, and 40 to the placebo. At the time of enrollment, there were no significant differences between the 3 groups in age, sex, weight, or length, and at end of the study, there were no significant differences in length of participation (Table 1). Subjects consumed formula and participated in the study for a range of 17–565 d (± SD: 210 ± 127 d of formula consumption; median: 192 d). The total time of formula consumption was 114 d for 25% of the infants studied, 192 d for 50%, and 268 d for 75%. The aggregate time of study was 24,830 subject-days (68 subject-years). Of the 118 children constituting the study population, 51 were consuming formula at the time of termination of the study and 67 had ended their participation before this. Of these 67, 42 had been naturally weaned from formula, mostly to whole milk; 19 had ended their participation because they left daycare; 3 had ended their participation because of parental perception of “dislike” for the formula; and 3 had ended their participation because of an effect perceived by their parents to be related to formula consumption. Of these 3, one infant developed a rash (after consuming the HS formula for 30 d); the rash was diagnosed as being viral by the pediatrician, persisted for 5 d after formula discontinuation, and then resolved. The second infant had loose stools and the third had loose stools and vomiting (both in the HS group).

Of the weekly phone calls for data collection, 3334 (93.9% of expected) were completed, with no significant difference between the groups (HS, 93.5%; LS, 93.1%; placebo, 95.2%). A total of 3404 daycare visits were completed (95.7% of expected; HS, 95.7%; LS, 96.2%; placebo, 95.2%), with no significant difference between groups. Weight and length were obtained monthly for all subjects; 97.9% of expected measures were completed, with no significant differences between the study groups.

Formula consumption

The study formulas were generally well accepted by both care providers and subjects. The mean amount of formula consumed per subject throughout the study period was 762 mL/d. Mean overall consumption and the range of consumption was not significantly different between the groups (Table 1). As expected, consumption varied with age, decreasing as the infants got older. The ranges of intake at 3, 6, 12, and 18 mo [kJ · kg⁻¹ · d⁻¹ (kcal · kg⁻¹ · d⁻¹)] were as follows: 225.9–698 (54–167), 83.7–548.1 (20–131), 54.4–343 (13–82), and 75.3–217.6 (18–52), respectively. Energy consumption from study formula was calculated by using the average formula consumption for the period ± 2 wk from the date on which monthly weight was obtained for each child. There were no significant differences in mean overall consumption or consumption by age for the 3 groups.

Bacterial consumption

On the basis of formula intake, body weight, and monthly microbial monitoring of formula, the weekly viable bacterial intake was calculated for each child throughout his or her participation in the study. The average amount of B. lactis consumed per subject at different ages is shown in Figure 1. The mean cumulative bacterial load and range for the HS and LS groups over the study period is shown in Table 2. Cumulative consumption per subject (total bacterial load ingested over the time of study) averaged 9.7 × 10⁷ CFU/kg for the LS group and 1.3 × 10⁸ CFU/kg for the HS group. The highest cumulative intake by a single subject was 4.9 × 10⁹ CFU/kg.

Growth

Shown in Table 3 are the SD (z) scores for weight/age, height/age, and weight/length at the time of enrollment and at the end of participation as well as the change in z scores over the time of participation for all subjects in each group. No child’s growth points were below the 5th percentile of the National Center for Health Statistics reference at any time during the study. Growth occurred in all groups (positive z score change), with no significant differences between the groups.

Clinical outcomes

The frequency of parental reporting of clinical signs and related symptoms and other general measures of health status and gastrointestinal symptoms by group are shown in Table 4. There was no significant difference in the frequency of reporting of loose stools, fever and vomiting associated with loose or watery stools, or discomfort passing bowel movements. The frequency of reporting of colic or irritability was significantly lower in both supplemented groups than in the placebo group (P < 0.001). Among general indicators of health status, no
significant differences were found in daycare absenteeism as a result of illness or in the frequency of health care attention. However, the frequency of reported use of antibiotics was significantly lower in both supplemented groups than in the placebo group.

DISCUSSION

The consumption of bacteria as part of the diet, mostly in the form of yogurt and other fermented milk products, has increased over the past decade, in part because of the broader availability of these foods but also because of the popular view of yogurt and similar products as healthy foods. Fermented milk products are a common part of the diet in Asia, Europe, and parts of Africa, and increasingly in North America. The consumption of nonpathogenic, lactic acid–producing bacteria as part of the diet for their potential beneficial effects has been dietary practice for centuries; the scientific literature referring to probiotic agents has increased dramatically over the past decade (3, 5, 9). Studies have shown beneficial effects of

TABLE 2
Consumption of *Bifidobacterium lactis* by the subjects throughout the study period

<table>
<thead>
<tr>
<th></th>
<th>HS group (n = 1225 observations)</th>
<th>LS group (n = 1026 observations)</th>
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<tbody>
<tr>
<td>Daily <em>B. lactis</em> consumption (CFU/kg body wt)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range per subject</td>
<td>1.9 × 10⁶ to 5.2 × 10⁸</td>
<td>2.9 × 10⁶ to 2.3 × 10⁷</td>
</tr>
<tr>
<td>Mean (± SD) per subject</td>
<td>4.1 × 10⁷ ± 5.4 × 10⁷</td>
<td>3.7 × 10⁶ ± 4.3 × 10⁶</td>
</tr>
<tr>
<td>Total cumulative <em>B. lactis</em> load consumed over the study period (CFU/kg body wt)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range per subject</td>
<td>2.4 × 10⁷ to 4.9 × 10⁸</td>
<td>1.3 × 10⁶ to 3.3 × 10⁸</td>
</tr>
<tr>
<td>Mean (± SD) per subject</td>
<td>1.3 × 10⁷ ± 1.2 × 10⁷</td>
<td>9.7 × 10⁷ ± 9.4 × 10⁷</td>
</tr>
</tbody>
</table>

¹ HS, high-supplement formula (contained 1 × 10⁷ CFU/g each *B. lactis* and *Streptococcus thermophilus*); LS, low-supplement formula (contained 1 × 10⁷ CFU/g each *B. lactis* and *S. thermophilus*); CFU, colony-forming unit. There were no significant differences between groups by Student’s *t* test.
probiotic bacteria, principally lactobacilli and bifidobacteria in conditions such as lactose malabsorption in adults (10, 11) and children (12, 13) and in the treatment of *C. difficile*-associated diarrhea (14, 15).

Several studies have documented that a number of bifidobacterial species do survive GI digestion and transiently colonize the intestine of infants supplemented with bifidobacteria (16–18). There are probably multiple mechanisms of action of these agents, which are likely specific to the individual effect they have in each one of these conditions. Among these mechanisms are competition with other flora, including potential pathogens, and modulation of gut immunologic mechanisms (19, 20).

Among the probiotic agents most commonly used are bifidobacteria and lactobacilli, in isolated forms or in combination. Many different strains and dosage patterns have been reported. The doses at which these agents have been used for potential clinical effects have varied, but generally fluctuate in the range of $1 \times 10^9$–$1 \times 10^{11}$ CFU given orally. The spectrum of subjects used in these studies is broad, ranging from healthy volunteers to oncologic patients and from premature infants to children with acute enteritis. However, the length of treatment in these studies has generally been short, usually <2 wk. Studies documenting long-term intakes in populations have predominantly been retrospective.

Bifidobacteria form the greater part of the intestinal flora of breastfed infants (21). In animals (22), bifidobacteria have been shown to be effective in improving the course of acute rotaviral diarrhea. Using the same infant formula product supplemented with *B. lactis* (Bb 12) and *S. thermophilus*, we reported a decreased incidence of diarrheal disease and rotaviral shedding in a group of hospitalized infants (23). Formulas containing *B. lactis* and *S. thermophilus* have been marketed in Europe, Asia, and South America for years, without any known adverse effects. Given centuries of use in the food supply, there has generally been little concern regarding the safety of these agents. Although exceptional, there have been several reports of bacteremia associated with selected probiotic bacteria. Endocarditis, pneumonia, and meningitis have very rarely been reported in association with lactobacilli, and extraordinary reports have been documented with *B. eikosoni* (6). No other study done with bifidobacteria or *B. lactis* has shown any adverse events. Most of these isolated reports, however, were in significantly compromised hosts, and we are not aware of any infections ever reported with other bifidobacteria or *S. thermophilus*.

Prospective studies specifically using *B. lactis* (20, 23) showed adequate growth. In children followed prospectively for various clinical indexes while receiving bifidobacteria, no apparent problems with growth were reported (24–26). However, safety, gastrointestinal tolerance, and growth with long-term use of probiotic-supplemented products have not been adequately studied for most of the probiotic agents currently available for human consumption. Additionally, many of these products are sold with no regulatory control (27, 28). Studies are even scarcer in pediatric populations. The present study specifically addressed these issues.

Reporting of loose stools and indicators of severity (including fever or vomiting associated with loose and watery stools) were not significantly different between the groups. From the point of view of gastrointestinal tolerance, there was a lower reported frequency of colic or irritability associated with probiotic use. Probiotics may, by modifying patterns of fermenta-

### TABLE 3

<table>
<thead>
<tr>
<th>Variables of general health and gastrointestinal tolerance†</th>
<th>HS group (n = 39)</th>
<th>LS group (n = 39)</th>
<th>Placebo group (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodes of loose or watery stools</td>
<td>1.68 (1.40, 1.96)</td>
<td>1.87 (1.55, 2.19)</td>
<td>1.96 (1.64, 2.28)</td>
</tr>
<tr>
<td>Episodes of emesis or fever with loose or watery stools</td>
<td>0.724 (0.53, 0.92)</td>
<td>0.59 (0.42, 0.75)</td>
<td>0.78 (0.23, 1.32)</td>
</tr>
<tr>
<td>Discomfort with bowel movement</td>
<td>0.86 (0.66, 1.06)</td>
<td>0.72 (0.52, 0.92)</td>
<td>0.70 (0.50, 0.90)</td>
</tr>
<tr>
<td>Colic or irritability†</td>
<td>4.71 (4.25, 5.19)</td>
<td>4.42 (3.99, 4.85)</td>
<td>5.7 (5.16, 6.21)</td>
</tr>
<tr>
<td>Use of antibiotics‡</td>
<td>3.19 (2.81, 3.56)</td>
<td>2.47 (2.11, 2.84)</td>
<td>3.60 (3.17, 4.02)</td>
</tr>
<tr>
<td>Health care attention for illness</td>
<td>2.55 (2.21, 2.89)</td>
<td>2.40 (2.04, 2.76)</td>
<td>2.94 (2.55, 3.33)</td>
</tr>
<tr>
<td>Daycare absenteeism due to illness</td>
<td>1.86 (1.57, 2.15)</td>
<td>2.07 (1.74, 2.41)</td>
<td>1.89 (1.57, 2.20)</td>
</tr>
</tbody>
</table>

† Values are frequency (95% CI) reported per 100 subject-days. HS, high-supplement formula (contained $1 \times 10^9$ colony-forming units/g each *Bifidobacterium lactis* and *Streptococcus thermophilus*); LS, low-supplement formula (contained $1 \times 10^6$ colony-forming units/g each *B. lactis* and *S. thermophilus*).

‡ Significantly lower in both supplemented groups than in the placebo group, *P* < 0.001 (Pearson’s chi-square test).
tion, lead to less gas or water formation, which in turn may affect gastrointestinal tolerance, although this remains speculative.

In terms of general health indicators, all children showed normal growth, and the population as a whole had no significant change in SD scores for ponderal and linear gain. The frequency with which health care attention was sought for illness and the reported frequency of antibiotic use was lower for both supplemented groups than for the placebo group, although only the difference in antibiotic use was significant \((P < 0.001)\). Several studies using probiotic agents, including \textit{B. lactis}, have documented several immunologic effects of probiotics, including increases in secretory immunoglobulin A (25, 29) and enhancement of phagocytic activity (30–32). In addition, the protective effect of probiotics in infectious and inflammatory conditions has been shown. Several studies documented efficacy with several strains of bifidobacteria, in isolation or together with other probiotics (33–35), all showing a shortened duration and generally a less complicated course of acute diarrheal disease in young infants in different settings.

Interest also has emerged in the area of probiotic use in the treatment and prevention of allergic disease, in particular, atopic dermatitis (36). Isolaurei et al (20) showed that infants receiving an extremely hydrolyzed formula supplemented with \textit{Lactobacillus GG} and \textit{B. lactis}, compared with a control group receiving only extremely hydrolyzed formula, showed significant improvement in signs of skin atopy. The association between food and atopic disease has lead to work in understanding and preventing nutrient and gut interactions leading to allergic symptoms (37–39). The immune-mediated benefits seen in the trials mentioned may be reflected by the decreased use of antibiotic agents in the present healthy infant population.

The study formula was well accepted by the parents and the care providers, and the children tolerated both supplemented formulas without any apparent problems. Formula consumption was as expected, with energy intake from formula gradually decreasing with subject age. The intake of bacteria from the product decreased accordingly by 0.5 log CFU/kg body wt for both supplemented groups at 1 y of age. On the basis of this intake, mean daily bacterial consumption and cumulative consumption over the study period were calculated for each subject. Mean intakes were up to \(4 \times 10^7\) CFU \(\cdot\) kg body wt \(^{-1}\) \(\cdot\) d \(^{-1}\) and the cumulative bacterial load ingested over time was as high as \(1.3 \times 10^9\) CFU/kg. Median daily average and cumulative bacterial load intakes were \(2.7 \times 10^7\) CFU \(\cdot\) kg \(^{-1}\) \(\cdot\) d \(^{-1}\) and \(1.1 \times 10^8\) CFU/kg, respectively. For those clinical outcomes for which trends or statistical differences were identified, the level of supplementation did not suggest a specific dose response.

The average child in this study consumed 7–8 log CFU live probiotic bacteria \(\cdot\) kg body wt \(^{-1}\) \(\cdot\) d \(^{-1}\) for 7 consecutive months. The highest absolute intakes and highest intakes per kilogram occurred in the youngest children because of higher formula intakes and lower body weights. This is further reassurance that even in very young populations, significant consumption of this specific combination of organisms is well accepted and safe.

To our knowledge, this is the first careful documentation of intake of live bacteria over any extended period of time in any population. The intakes studied can be used as a benchmark for well-tolerated, safe intake of these bacterial agents.

In conclusion, prolonged consumption by healthy infants of 2 formulas supplemented with live \textit{B. lactis} (Bb12) and \textit{S. thermophilus} at concentrations similar to those previously shown to have clinical benefits was studied. Consumption of bacterial loads in this population were as high as \(1 \times 10^6\) CFU \(\cdot\) kg \(^{-1}\) \(\cdot\) d \(^{-1}\) for periods of up to 1 y, with cumulative consumption over time of up to \(1 \times 10^7\) CFU/kg. Probiotic supplementation of these formulas resulted in adequate growth. The supplemented formulas were well accepted and tolerated and resulted in a significantly lower reported frequency of colic or irritability. Supplementation also resulted in a trend toward less frequent seeking of health care attention and a significantly lower frequency of antibiotic use.

The authors participated in the following aspects of this trial: JMS, design, execution, analysis, and manuscript writing; AA-H, design, execution, data management, analysis, and manuscript writing; NM, design, execution, data collection, data management, and manuscript writing; and RHY, design, analysis, and manuscript writing. None of the authors had a conflict of interest during the trial data analysis period.

REFERENCES

17. Bennet R, Nord CE, Zetterstrom R. Transient colonization of the gut...


