Prebiotics, Probiotics, and Synbiotics: Functional Foods

By Jacqueline J Wessel, MEd, RD, CNSD, CSP, CLE, LD

In the 1950s, my mother read books about nutrition, by authors such as Adele Davis, that espoused the concept of functional foods. Functional foods are those that have health benefits beyond that of their nutritional content. My mother in her stylish, cinched-waist cotton dresses (and high heels) made yogurt, which we all dutifully consumed for our health.

The concept of functional foods is now back. *Prebiotics* and *probiotics* are functional foods, and *synbiotics* are combinations of prebiotics and probiotics. The lining of the GI tract is important in host defense — the intestinal mucosa is on the front line between the host and the outside world. Keeping the mucosa intact and healthy is therefore important.

Probiotics

Probiotics may be the more familiar term to most people. The active culture component of yogurt is a probiotic. Fermented dairy foods such as yogurt and acidophilus milk are probably the most common probiotic-containing foods found in grocery stores. Although they have been used for many years, the term probiotic was just introduced in 1965.[1] The term is from the Greek "for life."[2] Probiotics are beneficial bacteria that exist in the healthy gut.[3] The colon is a reservoir of large quantities; an adult's large intestine has been estimated to contain about 500 different bacterial species,[3] some beneficial and others detrimental to health (see Table 1).

To be classified as a probiotic, a bacterial strain must be of human origin, be safe for human use, have its benefits proven scientifically, be stable in contact with acid and bile, and adhere to intestinal mucosa.[3,4] Probiotics have been shown in infants and children to decrease the duration of acute infectious diarrhea,[5-14] provide reasonable protection against antibiotic-associated diarrhea,[15-23] and perhaps play a role in prevention of food allergy in children at high risk of developing atopy.[24,25] In adults, certain strains of probiotics are effective in decreasing the symptoms of lactose intolerance.[4,26-28]

Probiotics have been studied in infants (6 to 36 months of age) as a strategy to lessen antibiotic-associated diarrhea (AAD), which may be mild to severe, and may start immediately or up to 6 weeks after antibiotics have been discontinued.[29] The disruption of normal fecal flora is thought to be the reason, with broad-spectrum antibiotics the most frequently implicated as causing AAD. Antibiotics affect the anaerobic component of fecal flora, which are considered to be responsible for protection against pathogenic proliferation. Beta-lactam antibiotics have been found most often associated with diarrhea.[30]

What about the possible role of probiotics and necrotizing enterocolitis (NEC)? Preterm infants have delayed establishment of gut flora.[31] Probiotics have been shown to modify colonic flora in infants, including VLBW infants.[32] In the preterm rat model, probiotics have been shown to reduce the rate of NEC.[33] The premature infant has an immature immune system, lower gastric acid production (the acid that could have killed bacteria), lower concentrations of protective mucus, lower proteolytic enzyme activity, and decreased gut motility; the premature infant is quite vulnerable to infection and inflammation.[34] One hypothesis about causation is that inappropriate colonization of bacteria can lead to NEC.[35] A

Table 1: Beneficial and Detrimental Bacteria[3]

Species	Beneficial	Detrimental
Bifidobacterium	+	
Eubacterium	+	
Lactobacillus	+	
Clostridium		+
Shigella		+
Veillonella		+

Some Probiotic Species

- *Bifidobacterium bifidum*
- *Bifidobacterium infantis*
- *Bifidobacterium breve*
- *Lactobacillus acidophilus*
- *Lactobacillus reuteri*
- *Lactobacillus rhamnosus*
- *Lactobacillus helveticus*
- *Streptococcus thermophilus*
- VSL#3, which consists of 8 bacterial strains: *Bifidobacterium*(B) *longum, B infantis, B breve, Lactobacillus* (L) *acidophilus, L casei, L bulgaricus, L planetarium, Streptococcus thermophilus*

systematic review by Barclay et al[36] in 2007 included studies with 1,191 infants (<1,500 gms), (see Table 2) and concluded that the data appeared to lend support to the use of probiotics for the prevention of NEC; however, the data were insufficient for comment on short- and long-term safety.[36] Another large study by *Hoyos* was not included in the analysis due to low scoring on methodology rating.[42] There have been isolated case reports of probiotic sepsis, although in the five studies reviewed by Barclay et al, no adverse reactions from probiotic sepsis were noted.[36] A new Cochrane review is supportive but recommends a large randomized trial to evaluate the potential benefits and safety profile of probiotics.[43]

A concern in the use of probiotics is whether the bacteria are able to reach the colon unscathed as they pass through gastric, pancreatic, and bile secretions to arrive in the colon to populate the gut.[44] The potential for sepsis[45,46] and the concern over viability of probiotics are two reasons that there is currently an emphasis instead on *prebiotic* research.

Prebiotics

Prebiotics are a concept that you may not have heard about, although again used in the 1950s (Lactulose was used 50 years ago as a prebiotic formula supplement to increase the numbers of *Lactobacillus* in infants' intestines).[47] The term prebiotic was first used by Gibson and Roberfroid in 1995.[48-50] A prebiotic is: "a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and activity of one or a limited number of bacteria in the colon."[51]

What is the difference between a probiotic and prebiotic? A probiotic introduces exogenous bacteria into the colon milieu; a prebiotic stimulates the growth of one or a limited number of the beneficial indigenous bacteria. Prebiotics change or modulate the composition of the natural ecosystem.[51]

What foods are prebiotics? Prebiotic activity has been seen in short-chain carbohydrates that are resistant to digestion in the upper GI tract but are hydrolyzed and fermented in the colon. Sometimes they are termed nondigestible oligosaccharides (NDOs).[4] See Table 3 for some of the prebiotics that have been studied.

Since *Bifidobacterium* is the predominant bacterium in breast-fed infants, much research has focused on possible prebiotics that would stimulate the growth of this organism. In adults, fructo-oligosaccharides (FOS)

Table 2: Five Studies Evaluating Probiotics and Necrotizing Enterocolitis (NEC)[36]

Study	Population	Number of Subjects	Organism and Quantity	Outcomes	Limitations
Dani et al. 2002[37]	Infants <33 weeks or BW <1,500 gm, 12 NICUs, Italy	295 treated, 290 placebo	*Lactobacillus GG* 6 x 10^9CFU in mother's milk, donor milk or preterm formula	Lower incidence of NEC: 1.45% treatment group vs 2.8% control (did not achieve statistical significance)	Low background incidence of NEC
Costalos et al. 2003[38]	Infants 28-33 weeks 2 NICU, Greece	51 treated, 36 placebo	*Saccaromyces boulardii* (10^9CFU in preterm formula)	Lower incidence of NEC: 9.8% treatment group vs. 16% control group of NEC (of any severity) but did not achieve statistical significance	Not powered to detect changes in NEC rates. Trend toward less NEC in treatment group (not significant statistically)
Lin et al. 2005[39]	Infants <1,500 gm 1 NICU, China	189 treated, 187 placebo	*Lactobacillus acidophilus* (1 million units) and *Bifidobacterium infantis* in mother's milk or donor milk	Lower incidence of all NEC: 1.1% vs. 5.3% (*P*= 0.04)	Any NEC primary outcome, although BELL stage ≥ 2 reported
Bin-Nun et al. 2005[40]	143 infants <1,500 gm, Israel	71 treated, 72 placebo	(10^9 CFU) *Bifidobacterium(B) bifidus, B infantis, Streptococcus thermophilus* in mother's milk or preterm formula	Lower incidence of all NEC in the treatment group 4% vs. 16.6% (*P*=0.031)	Combined outcome of NEC or death or sepsis measured
Manzoni et al. 2002[41]	80 infants <1,500 gm, 1 NICU, Italy	39 treated, 41 placebo	*Lactobacillus (GG* 6 x 10^9 CFU) in mother's or donor milk	Lower incidence of NEC in the treatment group 2.6% vs. 4.9%, non-significant trend (*P*=0.051)	Not powered to detect changes in NEC rates. Trend toward less NEC in treatment group (not significant statistically)

Table 3: Prebiotics

Type	Abbreviation	Type	Abbreviation
Fructo-oligosaccharide	FOS	Acacia gum	GUM
Inulin	None	Lactulose	LOS
Galacto-oligosaccharide	*GOS*	Lactitol	None
Polydextrose	PDX		

Table 4: Review of Studies using Prebiotic-Supplemented Formulas

Study	Population	Prebiotic and Quantity	Outcomes
Moro et al. 2002[56]	90 FAGA infants	0.4 g/dL, 0.8g/dL FOS, GOS and control	Dose dependent stimulating effect on *Bifidobacteria* and *Lactobacilli*, and softer stool No intolerance noted
Boehm et al. 2002[65]	42 Preterm infants <32 weeks	0.1 g/dL GOS/FOS and formula and breast-fed controls	*Bifidobacterium* significantly increased, similar to breast-fed infants Stool frequency significantly lower in control group No effect on tolerance or weight/length gain
Ben et al. 2004[66]	271 FAGA infants	0.24 g/dL GOS or control	Stool content of *Lactobacilli* and *Bifidobacterium* higher, similar to breast-fed infant No side effects noted
Bakker-Zierikzee et al. 2005[67]	57 FAGA infants + additional 63 controls	0.6 g/dL FOS and GOS or *B. animalis* or formula, 63 breast-fed controls	Breast-fed or FOS/GOS infants had similar flora Probiotic and control formula group had similar flora
Euler et al. 2005[68]	87 FAGA infants in a cross-over design	0.15 or 0.3 g/dL FOS or human milk	FOS supplemented at 0.3 g/dL resulted in softer, more frequent stool Supplemented formula was safe but had minimal effect on fecal flora and *Clostridium difficile* toxin
Knol et al. 2005[69]	35 FAGA infants + 19 breastfed controls	0.8g/dL GOS and FOS or control	Addition of prebiotics had stimulating effect on the growth of *Bifidobacterium* and on the growth of intestinal flora; profile closer to breast-fed infants
Bruzzese et al. 2006[70]	281 FAGA infants	GOS/FOS or control	Infants on prebiotic formula had fewer episodes of acute diarrhea, fewer upper respiratory infections
Costalos et al. 2007[38]	140 FAGA infants	0.4 g/dL of GOS and FOS and control	Prebiotic formula well tolerated, normal growth Trend toward higher percentage of *Bifidobacterium* and lower percentage of *E. coli* in stool, suppresses *Clostridium* in stool
Moro et al. 2006[71]	259 infants at risk for atopy	0.8 g/dL of GOS and FOS and control hydrolysed protein formula	Incidence of atopic dermatitis significantly reduced in the infants fed prebiotic formula
Ziegler et al. 2007[55]	226 FAGA infants	0.4 g/dL PDX, GOS or 0.8 g/dL PDX, GOS, and LOS or control	Looser stools on either prebiotic formula More adverse events: diarrhea, eczema, and irritability noted in supplemented groups
Scholtens et al. 2008[72]	215 FAGA infants	0.6 gm/dL FOS and GOS	At 26 weeks, the concentration of secretory IgA was higher in prebiotic group than control, also *Bifidobacterium* percentage higher than control and *Clostridium* lower
Arslanoglu et al. 2008[73]	152 FAGA infants	0.8 g/dL GOS/FOS	Formula fed for first 6 months; follow-up continued for 2 years. Prebiotic group had significantly lower allergic symptoms – atopic dermatitis, wheezing, urticaria, fewer upper respiratory infections than controls during the first 2 years

Key: FAGA—full-term appropriate for gestational age; GOS—galacto-oligosaccharides; FOS—fructo-oligosaccharides; PDX—Polydextrose; LOS—Lactulose.

have been shown to result in numerical predominance of *Bifidobacteria* in the stool.[48,52,53] In studies of rats colonized with human fecal flora, the use of galacto-oligosaccharide (GOS) has been shown to have similar effects.[54]

Formulas have been made with FOS and GOS for preterm, term, and weaning infants.[55,56] Table 4 reviews studies of prebiotic-supplemented formulas. Only the study by Ziegler had documented GI side effects.[56] GOS/FOS in formula appears to be well tolerated: the mixture appears to: (a) decrease diarrhea, (b) result in a softer stool, (c) be associated with fewer respiratory infections and atopic dermatitis symptoms, and (d) change the intestinal flora to that similar to the breast-fed infant. Investigators have also found other benefits: that certain prebiotics may decrease the growth of certain pathogenic bacteria, again trying to make the colonic bacterial mix optimal for health. For example, cellobiose has the ability to attenuate the virulence of *Listeria*.[57]

Prebiotics are substrates for fermentation and are thought to aid in the regulation of colonic function by increasing fecal bulk and water retention through the increased bacterial mass.

Synbiotics are substances that incorporate both pre- and probiotics.

Synbiotics

- *Bifidobacteria* and FOS
- *Lactobacilli* and lactitol
- *Bifidobacteria* and GOS

Neonatal Gastrointestinal Flora: Breast-fed versus Formula-fed

Where does it start? A baby before birth has a sterile GI tract. In a vaginal delivery, the baby is colonized, initially, with flora from the mother. The baby born by C-section is colonized with bacteria from the hospital environment instead of from the mother.[58,59] After birth, the intestinal flora is influenced by extrinsic factors; specifically, the type of feeding the baby receives is one factor that determines the composition of the GI flora.[58,59]

The intestinal flora of infants receiving breast milk is different from the flora of formula-fed infants. The flora of breast-fed infants is predominantly *Bifidobacteria* and *Lactobacilli*.[58] (This was noted in a work by Tissier in 1905.)[60] This microbial pattern is thought to have beneficial effects on the development of the immune system and exert a beneficial effect on intestinal function. Formula-fed babies have been noted to have more diverse flora, with larger numbers of *Enterobacteriaceae* and gram-negative organisms.[4,58]

Why do breast-fed babies have different colonies of bacteria? Human milk possesses oligosaccharides that have been identified as a "bifidogenic" factor — prebiotics! These carbohydrates have been found to be resistant to enzymatic degradation in the upper gastrointestinal tract. Why do breast-fed infants have fewer colonies of gram-negative bacteria? *Bifidobacteria* and *Lactobacilli* produce short-chain fatty acids, including lactic and other organic acids that lower colonic pH and inhibit the growth of some pathogenic bacteria. A commonly held belief is that *Bifidobacteria* produce a balanced and appropriate stimulation of the infant immune system.[4]

Uses for Prebiotics and Probiotics

What is the future of the use of prebiotics and probiotics? The use of such functional foods appears very promising. In the United States we are slower to come to the concept of functional foods for infants; for more than 10 years, the majority of infant formulas in Japan have contained prebiotics;[55,61,62] and they have been used in Europe for the past seven years.[62]

Clearly, breast milk is the "gold standard" for neonatal and infant nutrition and is recommended by the American Academy of Pediatrics as the nutrition of choice in the first year of life.[63,64] However, use of prebiotic-supplemented infant formulas may have benefits for the infant who does not receive mother's milk, for whatever reason. As seen in the study outcomes in Table 4, the benefits from prebiotic-supplemented formulas included:

1. Higher counts of *Bifidobacteria* by 4 weeks of age.
2. An increased number of *Bifidobacteria* is associated with lower numbers of intestinal pathogens.
3. The pattern of bifidobacterial subspecies is similar to the pattern of the breast-fed infant.
4. Prebiotic formulas result in stool pH and short-chain fatty acid patterns similar to the breast-fed infant.
5. Stool frequency and consistency is more like the breast-fed infant.
6. Reduced allergic reaction (atopic dermatitis) and reduced URI in the first year of life.
7. Fewer episodes of acute diarrhea.
8. Prebiotic-supplemented formula is easily tolerated, with no difference in growth patterns.

There are some things to consider as you see reports in the literature and read studies on these functional foods. You cannot safely extrapolate the effect on adults to infants, especially to preterm infants. Further, the action of one probiotic or prebiotic cannot be compared to that of another. The *amount* of pro- and prebiotics used in a study should also be similar for a valid comparison. This is a fascinating area of research, and one that may prove beneficial to our patients and their care givers.

About the Author

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