

A Primer on Prebiotics and Probiotics

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Prebiotic:

- “A nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health” (1995)¹
- *A more recent definition by the same author:* “A selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microflora, that confer benefits upon host well-being and health” (2004)²

Criteria for Prebiotic Classification²

1. **Resistance** to gastric acidity, enzyme hydrolysis, and gastrointestinal (GI) absorption
2. **Fermentation** by intestinal microflora
3. **Selective stimulation of growth** and/or activity of intestinal bacteria that contribute to health and well-being

Prebiotic Candidates and Sources

- Inulin and fructooligosaccharides (FOS)³: found in human breast milk and in foods such as asparagus, bananas, leeks, onions, garlic, wheat, chicory, tomatoes, and Jerusalem artichoke⁴
- (*trans*-) galactooligosaccharides (TOS or GOS)³: a mixture of oligosaccharides derived from lactose⁴ that can be found in supplemented foods and supplemented infant formula
- Other candidates with preliminary data³ include: gluco-, isomalto-, xylo-, and soybean oligosaccharides, lactosucrose, and polydextrose

Benefits of Probiotics for Infants

- Stimulate the growth of bifidobacteria⁴
- Increase stool softness and frequency similar to that of breast-fed infants^{5,6}
- Promote development of the immune system
- Positively affect postnatal immune development and increase fecal secretory IgA in infants⁷
 - Modulate immunological processes at the level of gut-associated lymphoid tissue⁷
- May help reduce infection rates, including respiratory infections and infections requiring antibiotics⁸
- Aid in immune system development⁴
 - Bifidobacteria colonization similar to that found within gut of breast-fed infants
 - Inhibit the growth of harmful bacteria by increasing beneficial bacteria population
- May help increase iron absorption⁹

Prebiotics and Atopic Dermatitis

- GOS/FOS added to infant formula decreases risk for atopic dermatitis (AD) and infections in high-risk infants
- Moro G et al, 2006¹⁰: N = 259
 - GOS/FOS group: 10 infants developed AD (9.8%; 95% CI 5.4–17.1%)
 - Placebo group: 24 infants developed AD (23.1%; 95% CI 16.0–32.1%)
- Arslanoglu S et al, 2008¹¹: Decreased cumulative incidences of AD, recurrent wheezing, and urticaria (*P* <0.05; N = 134)
 - GOS/FOS group: 13.6, 7.6, and 1.5%, respectively
 - Placebo group: 27.9, 20.6, and 10.3%, respectively

Possible Risks

- Study of newborn rat pups (animal model of preterm infants) and GOS/FOS¹²:
 - Increased incidence of translocation of aerobic and anaerobic bacteria noted in GOS/FOS-fed pups (25% versus 67%, *P* = 0.04; 50% versus 83%, *P* = 0.09)
 - Conclusion: GOS/FOS supplementation may not be beneficial for infants with highly immature intestines

Probiotics: Live microorganisms that, when ingested in adequate amounts, may beneficially affect the host¹³

Probiotics: Mechanisms of Action¹⁴

- Direct effects on epithelial cell function and intestinal health, including the:
 - Enhancement of epithelial barrier function
 - Modulation of epithelial cytokine secretion
 - Alteration of mucus production
 - Changing of bacterial luminal flora
 - Modification of the innate and systemic immune system
 - Induction of regulatory T-cell effects
- Probiotics are also able to reduce GI inflammation by exerting positive effects on epithelial cell and mucosal immune dysfunction

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Commonly Used Probiotics^{15,16}:

- *Bifidobacterium (bifidum, breve, infantis, longum)*
- *Streptococcus thermophilus*
- *Lactobacillus (acidophilus, casei, plantarum, reuteri, rhamnosus, rhamnosus ssp. GG)*
- *Lactococcus (lactis, cremoris)*
- *Escherichia coli (Nissle 1917)*
- *Saccharomyces (boulardii, cerevisiae)*
- Combination therapies

Probiotic Therapy in Gastroenterology: Challenges for Use in Children

- Stability
- Palatability
- Dosages, timing
- Compliance
- Safety

Positive Impact of Probiotics

- **Level I evidence**
 - Acute diarrhea: mainly lactobacilli, ≥10 billion/dose¹⁷
 - Allergy and atopic dermatitis (prevention)
 - Antibiotic-associated diarrhea: *S boulardii* and LGG¹⁷
 - Rotavirus diarrhea¹⁷
 - *Clostridium difficile* diarrhea: *S boulardii* and LGG¹⁷
 - *Helicobacter pylori* gastritis¹⁸
 - Pouchitis: mixture of lactobacilli strains, bifidobacteria, and *S thermophilus*¹⁷
 - Necrotizing enterocolitis^{19,20}
 - Ulcerative colitis¹⁷
- **Level II or III evidence**
 - Inflammatory bowel diseases¹⁷
 - Irritable bowel syndrome¹⁷
 - Bacterial overgrowth¹⁷
 - Lactose intolerance¹⁷

Quality of evidence categories¹⁷

- Evidence obtained from at least one properly designed randomized controlled study
- Evidence obtained from well-designed cohort or case-controlled trials (without randomization or from more than one center or research group) or from multiple time series with or without the intervention
- Evidence obtained from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Probiotic Data in Infants and Children: What Has Been Studied?

Scenario	Probiotics Studied
Breast-fed healthy child weaning to formula	<i>Bifidobacterium</i> sp. <i>Lactobacillus</i> sp.
Recurrent antibiotic-associated diarrheal infections	<i>L rhamnosus</i> ²¹
Viral diarrheal infections (eg, rotavirus)	LGG ²² Probiotic mixture of lactobacilli [4 strains], bifidobacteria [3 strains], and <i>S thermophilus</i> ²³
Preterm infants on broad-spectrum antimicrobials and parenteral nutrition	<i>B longum</i> and LGG do not accelerate weaning from IV nutrition or improve enteral tolerance in preterm infants weighing <1500 g ²⁴
Acute diarrhea in hospitalized children	Combination <i>Bacillus mesentericus</i> , <i>Streptococcus faecalis</i> , and <i>Clostridium butyricum</i> (attenuated the severity of acute diarrhea) ²⁵

Do Probiotics Reduce Diarrhea in Children? Results from 5 Meta-analyses:

Meta-analysis	Number of Trials	Number of Subjects	Outcome
Szajewska H, et al. (2001) ²⁶	23	1,900	↓ risk of diarrhea lasting >3 days
Van Niel CW, et al. (2002) ²⁷	9	765	↓ duration: 0.7 days
Huang JS, et al. (2002) ²⁸	13	1,113	↓ duration: 0.8 days
Szajewska H, et al. (2007) ²⁹	5	619	↓ duration: 1.1 days
Szajewska H, et al. (2007) ³⁰	8	988	↓ duration: 1.1 days

Probiotics and Necrotizing Enterocolitis (NEC)

Study	Probiotic	NEC Incidence: Probiotic Group	NEC Incidence: Control Group	RR	Favors Treatment or Favors Control (Fixed RR; 95% CI) ³¹
Bin-Nun A (2005) ³²	<i>B infantis/bifidus</i>	1/72 (1.4%)	10/73 (13.7%)	0.10	Favors treatment (0.01–0.1)
Costalos C (2003) ³³	<i>S boulardii</i>	5/51 (9.8%)	6/36 (16.7%)	0.59	Favors treatment (0.1–1)
Dani C (2002) ³⁴	LGG	4/295 (1.4%)	8/290 (2.8%)	0.49	Favors treatment (0.1–1)
Kitajima H (1997) ³⁵	<i>B breve</i>	0/45 (0%)	0/46 (0%)	NA	Favors treatment (0.1–1)
Lin HC (2005) ³⁶	<i>L acidophilus</i> ; <i>B infantis</i>	2/180 (1.1%)	10/187 (5.3%)	0.21	Favors treatment (0.1–1)
Manzoni P (2006) ³⁷	<i>L rhamnosus</i>	1/39 (2.6%)	3/41 (7.3%)	0.35	Favors treatment (0.1–1)
Mohan R (2006) ³⁸	<i>B lactis</i>	2/21 (9.5%)	1/17 (5.9%)	1.62	Favors control (1-5)
Total events: 15 (probiotic), 38 (no probiotic)		Test for heterogeneity: X ² =4.66, df=5(P=0.46), I ² =0%		Total RR (95% CI) = 0.36	

CI = confidence interval; RR = relative risk

Reviewed in: Deshpande G, et al. *Lancet*. 2007;369:1614-1620.³¹

Confirmed by: Barclay S, et al. *J Pediatr Gastroenterol Nutr*. 2007;45:569-576.³⁹

Possible Complications of Probiotic Therapy

- Risk factors: underlying immune compromise, chronic disease, or debilitation⁴⁰
 - No reports of probiotic-related sepsis in healthy persons
- Complications reported in infants/children treated with probiotics: bacteremia, endocarditis, fungemia, meningitis, septicemia, and fungemic shock⁴⁰
 - Implicated probiotics: bifidobacterium (1 case), *S boulardii*, LGG
 - Most cases resolve with appropriate antimicrobial therapy
- Studies have determined probiotics such as *B lactis* and *S thermophilus* to be safe and well tolerated in infant formula⁴¹

Complications of Probiotic Therapy: Children and Infants

Form of Sepsis	Age	Risk Factors	Probiotic	Reference
Fungemia	1 yr	AAD, CVC, TPN	<i>S boulardii</i>	Pletincx M. <i>JPGN</i> . 1995;21:113-115. ⁴²
Endocarditis	4 mo	AAD, cardiac surgery	LGG	Land MH. <i>Pediatrics</i> . 2005;115:178-18. ⁴³
Meningitis	37 days	None known	<i>B breve</i>	Hata D. <i>Pediatr Infect Dis J</i> . 1988;7:669-671. ⁴⁴
Bacteremia	3 mo;	Prematurity, SGS;	LGG	Kunz AN. <i>JPGN</i> . 2004;38:457-458. ⁴⁵
	11 wks	Prematurity, SGS, inflamed intestine		
	6 y	AAD, CP, CVC, jejunostomy		
	11 mo	CVC, prematurity, gastrostomy, rotavirus, SGS, TPN	LGG	De Groot MA. <i>Pediatr Infect Dis J</i> . 2005;24:278-280. ⁴⁶

AAD = antibiotic-associated diarrhea; CP = cerebral palsy;

CVC = central venous catheter; *JPGN* = *J Pediatr Gastroenterol Nutr*;

LGG = *Lactobacillus GG*; SGS = short gut syndrome; TPN = total parenteral nutrition

Reviewed in: Boyle R, et al. *Am J Clin Nutr*. 2006;83:1256-1264.⁴⁷

Probiotics: Late Complications?

- LGG administered to mothers prior to delivery and then to infants shortly after delivery:
 - Decreased incidence of AD in the LGG group
 - Increased incidence of allergic rhinitis and asthma in LGG group at 7 years⁴⁸
- At 2 years of age, there was no difference in AD incidence between groups, but there was a statistically significant increase in wheezing bronchitis (26% versus 9%) in the LGG-treated group⁴⁹
 - At 12 months, the rate of sensitization to common allergens was significantly higher in the probiotic group⁵⁰

Conclusions

- The intestinal microbiota interact closely with innate and adaptive mucosal immune systems; manipulation of the microbiota may alter long-term health (eg, affect development of disorders such as autoimmune diseases, allergy, asthma).
- Preliminary data support the potential of prebiotics as dietary manipulation for improving the immune system and GI microflora during infancy, and for the prevention of certain diseases such as allergies and AD; however, further studies are needed to better elucidate the mechanism behind these effects.⁵¹
- Preliminary data also suggest that there are a number of conditions for which probiotics may be useful; however, more research must be done to standardize and regulate these agents in regard to dosing, strain specificity for disease, and safety.⁵²