

# IRRITABLE BOWEL SYNDROME AND PROBIOTICS

Irritable bowel syndrome (IBS) is a chronic disorder characterized by recurring symptoms of abdominal pain or discomfort and associated with disturbed defecation. It affects as many as one in five American adults and is among the most common syndromes seen by gastroenterologists and primary care providers. IBS occurs more frequently in women than in men; it is diagnosed before the age of 35 years in about half of patients.

## Table. Rome III Diagnostic Criteria for Irritable Bowel Syndrome

Recurrent abdominal pain or discomfort (an uncomfortable sensation not described as pain) at least 3 days per month in the past 3 months, associated with two or more of the following:

- Improvement with defecation.
- Onset associated with a change in frequency of stool.
- Onset associated with a change in form (appearance) of stool.

The criteria must be fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Source: Reprinted from Longstreth et al. (see REFERENCES) with permission from Elsevier.

IBS is referred to as a “functional disorder,” meaning that it has no known or detectable organic causes. The diagnosis is made on the basis of symptom-based criteria known as the “Rome criteria” (TABLE). IBS may be further categorized into one of three subtypes, according to the predominant bowel symptom:

- IBS with constipation (more common in women).
- IBS with diarrhea (more common in men).
- IBS with alternating symptoms of constipation and diarrhea.

Each group accounts for approximately one third of all patients.

IBS causes substantial discomfort and emotional distress. In addition to constipation, diarrhea, and abdominal pain, IBS symptoms may include cramping, bloating, fecal urgency, flatulence, a sense of incomplete evacuation, and straining. The symptoms can be unpredictable and disabling; some patients are unable to work, attend social events, or even travel short distances. Patients report a diminished quality of life similar to that reported by patients with diabetes or chronic renal failure. As many as 70% of patients with IBS do not seek or do not receive medical care for their symptoms (see IS IT IRRITABLE BOWEL SYNDROME?).

Currently, there is no cure for IBS, so treatment is aimed at controlling symptoms. Unfortunately, even symptomatic treatment is hindered by a dearth of truly effective therapies. The serotonergic medications tegaserod (Zelnorm®) and alosetron (Lotronex®)—both of which had been shown to improve patients’ overall quality of life and moderate many of the motor and sensory abnormalities associated with IBS—were withdrawn from the U.S. market following reports of serious adverse effects. (Alosetron currently is available through a restricted prescribing program only for the treatment of women with severe IBS with diarrhea; tegaserod is available for use in emergency situations only.) Lubiprostone (Amitiza®), a locally acting chloride channel activator, was approved in April 2008 for the treatment of IBS with constipation in women aged 18 years and older. It is not approved for use in men or for the treatment of other IBS subtypes.

There is strong and growing interest in probiotics as a promising therapeutic strategy for IBS. Researchers have reported significant alterations in the intestinal microbiota of patients with IBS, including a relative decrease in the number of bifidobacteria. Probiotics have the potential to influence many of the mechanisms that may underlie the symptoms of IBS, including immune function, intestinal motility, and the intraluminal milieu. A growing number of studies show probiotics to be a safe, convenient option for improving a wide variety of IBS symptoms.

## Is It Irritable Bowel Syndrome?

Pharmacists can ask the following questions to help detect patients with IBS:

- Do you have recurrent abdominal pain or discomfort?
- Do you often feel bloated?
- Are you frequently constipated?
- Do you have frequent diarrhea?

Any patient with one or more of these symptoms should be encouraged to consult with a health care provider.

Source: Adapted with permission from the American College of Gastroenterology.

# BIFIDOBACTERIUM INFANTIS 35624 (BIFANTIS®)

Species of *Bifidobacterium* account for up to 95% of the bacteria in the gastrointestinal tract of breastfed infants. The high proportion of bifidobacteria may be responsible for, or at least contribute to, the health benefits associated with breastfeeding. Although the percentage of bifidobacteria declines with age, they still account for up to 25% of the bacteria in the adult gastrointestinal tract.

*B. infantis* 35624 is a probiotic strain that was isolated from the resected intestinal epithelium of a healthy adult who underwent urinary tract reconstructive surgery. (Until that time, probiotic candidates had been isolated primarily from feces, rather than from the environment in which they eventually would be required to function.) It has a well-documented genome sequence with no known regions of pathogenicity. Two well-designed clinical trials have confirmed the ability of *B. infantis* 35624 to relieve many of the most troublesome symptoms of IBS.

In the first trial, O'Mahony and colleagues administered *B. infantis* 35624 or *Lactobacillus salivarius* UCC4331 in a malted milk drink—or the malted milk drink alone as a placebo—to 75 adults with IBS. Both bacteria were administered at a dose of  $1 \times 10^{10}$  live cells. The study subjects were asked to consume the drink each morning for 8 weeks and record informa-

tion about their symptoms and stool characteristics each day. Blood samples were obtained at the beginning and end of the study for measurement of cytokine levels.

During the treatment period, patients who received *B. infantis* 35624 had significantly lower scores most weeks for the three cardinal symptoms of IBS—pain/discomfort, bloating/distention, and bowel movement difficulty—than did patients who received placebo. Patients who received *L. salivarius* UCC4331 had significantly lower scores for abdominal pain only, during only 2 weeks of the treatment period. A direct comparison between the groups receiving *B. infantis* 35624 and *L. salivarius* UCC4331 showed significantly lower scores for bowel movement difficulty among patients receiving *B. infantis* 35624. All groups reported similar numbers of bowel movements and similar bowel movement consistency, indicating that the benefits of *B. infantis* 35624 treatment could not be attributed to either a laxative effect or an antidiarrheal effect.

At baseline, study subjects exhibited abnormally low levels of interleukin (IL)-10 and high levels of IL-12, compared with those of a group of age-matched and sex-matched healthy volunteers. These changes were consistent with a pro-inflammatory state. Cytokine levels were normalized (i.e., returned to levels similar

to those observed in healthy volunteers) only in patients who received *B. infantis* 35624, suggesting an immunomodulating role for this probiotic.

In the second trial, Whorwell and colleagues investigated the efficacy of an encapsulated formulation of *B. infantis* 35624 in women with IBS. A total of 362 women were randomized to receive one of three daily doses of *B. infantis* 35624 ( $1 \times 10^6$ ,  $1 \times 10^8$ , or  $1 \times 10^{10}$  CFU/mL) or placebo for 4 weeks. The women reported their symptoms daily using an interactive voice recording system.

Only one of the study doses— $1 \times 10^8$ —was associated with a significant improvement in abdominal pain/discomfort (the primary study variable) compared with placebo. This dose also was associated with significant improvements in the secondary study variables of bloating/distention, sense of incomplete evacuation, passage of gas, straining, and bowel habit satisfaction. The improvement in the score for bowel habit satisfaction was significant among patients with the constipation-predominant IBS subtype as well as patients with the diarrhea-predominant subtype. Positive responses to a global assessment of relief from both abdominal pain/discomfort and IBS symptoms at the end of therapy were more than 20% greater for *B. infantis* 35624 than for placebo.

## REFERENCES

- American College of Gastroenterology. *Understanding Irritable Bowel Syndrome: A Consumer Education Brochure*. Available at: <http://www.gi.org/patients/ibsrelief/IBS.pdf>. Accessed September 9, 2008.
- Camilleri M. Probiotics and irritable bowel syndrome: rationale, putative mechanisms, and evidence of clinical efficacy. *J Clin Gastroenterol*. 2006;40:264–9.
- Collins MD, Gibson GR. Probiotics, prebiotics, and synbiotics: approaches for modulating the microbial ecology of the gut. *Am J Clin Nutr*. 1999;69(suppl):1052S–1057S.
- Drossman DA, Camilleri M, Mayer EA, et al. AGA technical review on irritable bowel syndrome. *Gastroenterology*. 2002;123:2108–31.
- Dunne C, Murphy L, Flynn S, et al. Probiotics: from myth to reality. Demonstration of functionality in animal models of disease and in human clinical trials. *Antonie Van Leeuwenhoek*. 1999;76:279–92.
- Food and Drug Administration. FDA approves Amitiza for IBS-C [press release]. Rockville, MD: Food and Drug Administration; April 29, 2008. Available at: <http://www.fda.gov/bbs/topics/NEWS/2008/NEW01828.html>. Accessed September 28, 2008.
- Food and Drug Administration Web site. Lotronex (alosetron hydrochloride) information. Available at: <http://www.fda.gov/cder/drug/infopage/lotronex/lotronex.htm>. Accessed September 12, 2008.
- Food and Drug Administration Web site. Zelnorm (tegaserod maleate) information. Available at: <http://www.fda.gov/cder/drug/infopage/zelnorm/default.htm>. Accessed September 12, 2008.
- Gralnek IM, Hays RD, Kilbourne A, et al. The impact of irritable bowel syndrome on health-related quality of life. *Gastroenterology*. 2000;119:654–60.
- Hammerle CW, Surawicz CM. Updates on treatment of irritable bowel syndrome. *World J Gastroenterol*. 2008;14:2639–49.
- Huffnagle GB. *The Probiotics Revolution*. New York, NY: Bantam Books; 2007.
- Kassinen A, Krogus-Kurikka L, Mäkiyuokko H, et al. The fecal microbiota of irritable bowel syndrome patients differs significantly from that of healthy subjects. *Gastroenterology*. 2007;133:24–33.
- Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. *Gastroenterology*. 2006;130:1480–91.
- Madden JA, Hunter JO. A review of the role of the gut microflora in irritable bowel syndrome and the effects of probiotics. *Br J Nutr*. 2002;88(suppl 1):S67–S72.
- Malinen E, Rinttilä T, Kajander K, et al. Analysis of the fecal microbiota of irritable bowel patients and healthy controls with real-time PCR. *Am J Gastroenterol*. 2005;100:373–82.
- Mayer EA. Irritable bowel syndrome. *N Engl J Med*. 2008;358:1692–9.
- McFarland LV, Dublin S. Meta-analysis of probiotics for the treatment of irritable bowel syndrome. *World J Gastroenterol*. 2008;14:2650–61.
- National Digestive Diseases Information Clearinghouse. Irritable bowel syndrome. Available at: <http://digestive.niddk.nih.gov/ddiseases/pubs/ibs/>. Accessed September 9, 2008.
- O'Mahony L, McCarthy J, Kelly P, et al. *Lactobacillus* and *Bifidobacterium* in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. *Gastroenterology*. 2005;128:541–51.
- Parkes GC, Brostoff J, Whelan K, et al. Gastrointestinal microbiota in irritable bowel syndrome: their role in its pathogenesis and treatment. *Am J Gastroenterol*. 2008;103:1557–67.
- Quigley EM. Probiotics in irritable bowel syndrome: an immunomodulatory strategy? *J Am Coll Nutr*. 2007; 26:684S–690S.
- Whorwell PJ, Altringer L, Morel J, et al. Efficacy of an encapsulated probiotic *Bifidobacterium infantis* 35624 in women with irritable bowel syndrome. *Am J Gastroenterol*. 2006;101:1581–90.
- Zuccotti GV, Meneghin F, Raimondi C, et al. Probiotics in clinical practice: an overview. *J Int Med Res*. 2008;36(suppl 1):1A–53A.