# Recommendations for Probiotic Use—2015 Update

## *Proceedings and Consensus Opinion*

*Martin H. Floch, MD,* W. Allan Walker, MD,†,‡*
*on behalf of Mary Ellen Sanders, PhD,§ Max Nieuwdorp, MD, PhD,‖¶*
*Adam S. Kim, MD,# David A. Brenner, MD,** Amir A. Qamar, MD,††*
*Tamir A. Miloh, MD,‡‡§§‖‖ Alfredo Guarino, MD,¶¶ Mario Guslandi, MD,##*
*Levinus A. Dieleman, MD, PhD,*** Yehuda Ringel, MD,†††*
*Eamonn M.M. Quigley, MD,‡‡‡§§§ and Lawrence J. Brandt, MD‖‖‖*

**Abstract:** This paper describes the consensus opinion of the participants in the 4th Triennial Yale/Harvard Workshop on Probiotic Recommendations. The recommendations update those of the first 3 meetings that were published in 2006, 2008, and 2011. Recommendations for the use of probiotics in necrotizing enterocolitis, childhood diarrhea, inflammatory bowel disease, irritable bowel syndrome and *Clostridium difficile* diarrhea are reviewed. In addition, we have added recommendations for liver disease for the first time. As in previous publications, the recommendations are given as A, B, or C ratings.

**Key Words:** probiotics, probiotic use, recommendations

(*J Clin Gastroenterol* 2015;49:S69–S73)

From the *Department of Internal Medicine, Section of Digestive Diseases, Yale University School of Medicine, New Haven, CT; †Harvard Medical School; ‡Mucosal Immunology and Biology Research Center, Massachusetts General Hospital for Children, Boston; ††Department of Transplantation, Lahey Hospital and Medical Center, Burlington, MA; §Dairy & Food Culture Technologies, International Scientific Association of Probiotics and Prebiotics (ISAPP), Sacramento; **Department of Medicine, University of California, San Diego, San Diego, CA; ‖Departments of Internal Medicine, Academic Medical Center and VUmC, Amsterdam, The Netherlands; ¶Wallenberg Laboratory, Gothenborg University, Gothenburg, Sweden; #Minnesota Gastroenterology P.A., Minnesota, MN; ‡‡Pediatric Liver & Liver Transplant, Gastroenterology/Transplantation, Phoenix Children's Hospital; ‖‖Mayo Clinic, Phoenix; §§Department of Pediatrics, University of Arizona, Tucson, AZ; ¶¶Department of Translational Medical Sciences, Section of Pediatrics, University of Naples Federico II, Naples; ##Clinical Hepato-Gastroenterology Unit, Division of Gastroenterology & Digestive Endoscopy, S. Raffaele University Hospital, Milano, Italy; ***Division of Gastroenterology, University of Alberta, Edmonton, AB, Canada; †††Department of Gastroenterology, University of North Carolina School of Medicine, Chapel Hill, NC; ‡‡‡The Lynda K. and David M. Underwood Center for Digestive Disorders, Houston Methodist Hospital, Houston, TX; §§§Department of Medicine, Weill Cornell Medical College, New York; and ‖‖‖Department of Medicine and Surgery, Division of Gastroenterology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY.

M.H.F. is on the Scientific Advisory Committee (SAC) of Nature's Bounty and was previously on the Medical Board of Dannon. W.A.W. is supported by NIH grants (P30 DK040561, P01 DK033506, R01 HD012437, R01 HD059126, 3T32DK007191-39S1). The other authors declare that they have nothing to disclose.

Reprints: Martin H. Floch, MD, Department of Internal Medicine, Section of Digestive Diseases, Yale University School of Medicine, 333 Cedar Street, 1080 LMP, New Haven, CT 06510 (e-mail: martin.floch@yale.edu).

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

This supplement represents the results of the proceedings of the 4th Triennial Yale/Harvard Workshop on Probiotic Recommendations. Unfortunately, because of unforeseen personal illness, both Dr Floch and Dr Walker were unable to attend. However, this consensus is written by Dr Floch from the papers and approved by all of the faculty participants. Dr Mary Ellen Sanders was the moderator for the program. She gave her talk and also moderated the morning program and presented the conclusions from the meeting, whereas the afternoon was moderated by Dr Yehuda Ringel. We are indebted to Procter & Gamble, Sigma-tau, and Dannon for their major contributions in supporting this meeting and supplement, as they have in the past.

Dr Sanders gave the first talk,[1] and her paper covers the recent perspectives on the concept of probiotics, controls by regulatory agencies, as well as safety issues. Most importantly, she discusses the concept that, when mechanistic similarities are shared, probiotic benefits may be attributable to groups of strains rather than only be considered strain specific. This has implications for clinical recommendations and for reviewing the totality of evidence for a systematic review and meta-analysis.

The second paper in the supplement is by Dr Walker.[2] His presentation was not given at the meeting because he was unable to attend, but it is one of the most important papers to understand in detail for anyone working with probiotics. Dr Walker covers the immunologic relationship to the host from birth to the disease processes that may occur. The method of developing the relationship of the host to the microbiota is extremely important functionally and should be understood by anyone working in the field. He covers the immunologic responses and also how the disease process may occur. Finally, he carefully covers necrotizing enterocolitis, allergy, and atopy. This is an essential paper to understand the functional and disease relationships between the microbiota and the host.

The next presentation was by Dr Nieuwdorp. The actual paper has been written by Bakker et al.[3] It covers the material that was presented by Dr Nieuwdorp. He carefully presents the theories behind energy expenditure in health, disease, and obesity by the gut microbiota. This is fascinating material that should now become important in the field of obesity study, as well as the relationship of the microbiota to energy as it occurs in metabolic disturbances such as diabetes. Although microbiota dysbiosis is not yet proven in these areas, the alterations are suspicious in both



Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

weight loss and weight gain. This paper is important for the future study of weight balance and the potential role of novel probiotics derived from gut microbiota studies.

The next presentation and manuscript was given by Adam Kim,[4] who coauthored 2 recent textbooks on probiotics. The paper covers dysbiosis. In the manuscript and talk he attempted to define dysbiosis, which is still controversial, but he clearly defines the normal bacterial flora as accepted by the Human Microbiome Project[5] and then in detail covers the alterations of the bacterial flora as now reported in the obesity literature,[6] as well as in inflammatory bowel diseases[7] and other conditions. To understand probiotic therapy, one has to understand the alterations that occur to the microbiota and hope that the therapy corrects the dysbiosis and brings the host flora back to what is considered a normal microbiota.

The next part of this supplement deals with the liver. This subject was not covered in the last 3 meetings. The first talk was given by Dr David Brenner, who outlined the importance of alcohol and metabolic reactions in the liver, leading to liver failure and the use of probiotics in liver failure. He emphasized the role of the microbiota in liver pathophysiology.[8]

In the next presentation, Dr Amir Qamar reviews in detail the microbiota in liver disease and goes over the pathophysiology of microflora in hepatic encephalopathy, nonalcoholic fatty liver disease, and steatohepatitis.[9–16] In his discussion, he describes the pathologic mechanisms that are suspected and how the use of probiotics may be helpful by describing the probiotic literature in this area and the successful probiotic trials. This is a new approach for recommendation by the Yale/Harvard workshop faculty, which will be listed in Table 1. There is clearly an indication for recommendations even though they are still grade C to some but grade B to others.

In the next paper by Tamir Miloh[17] the same factors are described as they relate to children. He discussed the trials in managing children with nonalcoholic fatty liver disease and the success of some. He also points out that, in children, probiotics may be helpful in cystic fibrosis and definitely effective in necrotizing enterocolitis and familial hypercholesterolemia. His paper clearly describes the details of the literature, but he feels more data are needed from larger trials.

The next subject covered in the supplement and at the meeting was a review of treatment for diarrhea of acute gastroenteritis. Dr Guarino reviewed all of the previous data on the use of probiotics, and the recommendations have essentially not changed.[18] The most effective agents appear as recommended in Table 1 and include *Lactobacillus* GG and *Saccharomyces boulardii*.

The next presentation by Dr Mario Guslandi[19] discusses the use of probiotics in pouchitis and Crohn's disease. He covers the data that probiotics have been widely accepted for use in pouchitis but also takes on the problem of Crohn's disease, which is controversial. Probiotics themselves do not appear to be preventive or curative in Crohn's disease, but according to some are helpful in treatment. He also carefully reviews antibiotic-associated diarrhea and its use in prevention in *Clostridium difficile*.

The next subject on the use of probiotics in inflammatory bowel disease relates to ulcerative colitis.[20] This subject is carefully analyzed by Leo Dieleman. It is now widely accepted that probiotic therapy is helpful in ulcerative colitis treatment. He points out that only VSL#3 and *Escherichia coli* Nissle 1917 have shown benefit in excellent studies. He reviews the mechanisms in which they would be helpful, and our recommendations continue to be positive on this subject. The dysbiosis may occur as reported, but results do not clearly show a correction of the dysbiosis even though probiotics are effective clinically.

Dr Yehuda Ringel first analyzes the intestinal microbiota in irritable bowel syndrome (IBS)[21] and functional gastrointestinal disorders as he moderated the afternoon session. He describes the possible physiological mechanisms affecting brain and behavior and the ways that probiotics may treat the condition. He clearly points out that there is a dysbiosis in IBS and that it is assumed that correction of the dysbiosis may affect symptoms. There is a rationale for targeting the intestinal microbiota in the treatment of IBS. However, there are all too few consistent studies, and recommendations are, therefore, limited.

In the next presentation, Eamonn Quigley, who is one of the original authors supporting the use of *Bifidobacterium infantis* 35624, describes the many problems with selecting probiotics to treat this diverse clinical condition.[22] However, he points out that there is scientific evidence and a rationale for the use of probiotics in IBS, but larger and more studies are needed with different organisms.

The next presentation is on fecal microbiota transplant (FMT)[23] given by Dr Lawrence J. Brandt who has wide experience in treating these patients. It is clear from the literature he reviews that FMT works in treating severe recurrent *C. difficile* infection. In addition, the future holds a wide range of options. In this review of the literature, the first papers described include the early work by Dr Borody in Australia and now the use of voluntary donor fecal microbial combinations in pills as presented in the papers by Louie et al[24] and Youngster et al.[25] Dr Brandt discusses the possibility that this treatment can be used for other diseases. This is a historic time for FMT. The new works being presented in the literature should be exciting. The present recommendations continue that FMT works for the treatment of recurrent *C. difficile* diarrhea.

Table 1 presents the recommendations of the Yale/Harvard workshop faculty. This is an update to the previous table.[26] We include liver disease in the table for the first time. References are included, as well as the indications in hepatic encephalopathy, NAFLD, NASH, and childhood hypercholesterolemia.

Floch and Walker have written this consensus report, which is supported by all presenters.

Once again, we are indebted to Procter & Gamble, Sigma-tau, and Dannon for the major support of this meeting and supplement. We also thank Dr Sanders and Dr Ringel, who moderated the meeting in our absence.


Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

**TABLE 1.** Recommendations for Probiotic Use: Update 2015

| Clinical Condition | Effectiveness | Specific Strain of Organism and Strain References | References |
|---|---|---|---|
| Diarrhea | | | |
| Infectious childhood—treatment | A | LGG, *Saccharomyces boulardii*, *Lactobacillus reuteri* SD2112 | 27–30 |
| Prevention of infection | B | *S. boulardii*, LGG | 27,28,30 |
| Prevention of AAD | A | *S. boulardii*, LGG, combination of *L. casei* DN114 G01, *L. bulgaricus*, snf *Streptococcus thermophilus* | 31–33 |
| Prevention of recurrent CDAD | B/C | *S. boulardii*, LGG, FMT | 34–37 |
| Prevention of CDAD | B/C | LGG, *S. boulardii* | 34,37 |
| IBD | | | |
| Pouchitis | | | |
| Preventing and maintaining remission | A | VSL#3 | 38–40 |
| Induce remission | C | VSL#3 | 41 |
| Ulcerative colitis | | | |
| Inducing remission | B | *Escherichia coli* Nissle, VSL#3 | 42–44 |
| Maintenance | A | *E. coli* Nissle, VSL#3 | 43–45 |
| Crohn's | C | *E. coli* Nissle, *S. boulardii*, LGG | 46–48 |
| IBS | | | |
| | B | *Bifidobacterium infantis* B5624, VSL#3 | 49–53* |
| | C | *B. animalis* | 54 |
| | | *L. plantarum* 299V | 55 |
| Necrotizing enterocolitis | | | |
| | B | *L. acidophilus* NCDO1748, *B. bifidium* NCDO1453 | 56,57 |
| Recommendations from 2008† | | | |
| Immune response | | | |
| | A | *L. rhamnosus* GG, *L. acidophilus* LAFT1, *L. plantarum*, *B. lactis*, *L. johnsonii* | 58,59 |
| Allergy | | | |
| Atopic eczema associated with cow's milk allergy | | | |
| Treatment | A | LGG, *B. lactis* | 59 |
| Prevention | A | LGG, *B. lactis* | 59 |
| Radiation enteritis | | | |
| | C | VSL#3, *L. acidophilus* | 60,61 |
| Vaginosis and vaginitis | | | |
| | C | *L. acidophilus*, *L. rhamnosus* GR-1, *L. reuteri* RC14 | 62–64 |
| Recommendations from 2015 | | | |
| Liver disease | | | |
| Hepatic encephalopathy | A | VSL#3 | 8–12 |
| Nonalcoholic fatty liver disease | C | VSL#3, combinations of *L. plantarum*, *L. delbrueckii*, *L. bulgaricus*, *L. acidophilus*, *L. rhamnosus*, *B. bifidium*, *S. thermophilus*, *B. longum* | 8,9,13,15,16 |
| Nonalcoholic fatty liver disease in children | C | VSL#3, LGG | 17 |
| Alcoholic liver disease | C | VSL#3, LGG, *L. acidophilus*, *L. bulgaricus*, *B. bifidium*, *B. longum* with oligosaccharides | 8–17 |

*Guandalini et al[53] was made available after the workshop meeting on April 8, 2011, but believed to be significant enough to qualify this probiotic to be in a B category.

†Check 2008 references for further elaboration on strains used and their availability.

AAD indicates antibiotic-associated diarrhea; CDAD, *Clostridium difficile*-associated diarrhea; FMT, fecal microbiota transplant; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; LGG, *Lactobacillus* GG.

## REFERENCES


1. Sanders ME. Probiotics in 2015; their scope and use. *J Clin Gastroenterol*. 2015;49(suppl):S2–S6.
2. Houghteling PD, Walker WA. From birth to "immunohealth", allergies and enterocolitis. *J Clin Gastroenterol*. 2015; 49(suppl):S7–S12.
3. Bakker GJ, Zhao J, Herrema H, et al. Gut microbiota and energy expenditure in health and obesity. *J Clin Gastroenterol*. 2015;49(suppl):S13–S19.
4. Kim A. Dysbiosis; a review highlighting obesity and inflammatory bowel disease. *J Clin Gastroenterol*. 2015; 49(suppl):S20–S24.
5. Consortium HMP. Structure, function and diversity of the healthy human microbiome. *Nature*. 2012;486:207–214.
6. Turnbaugh PJ, Hamady M, Yatsunenko T, et al. A core gut microbiome in obese and lean twins. *Nature*. 2009;457: 480–484.
7. Loftus CG, Loftus EV, Harmsen WS, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940-2000. *Inflamm Bowel Dis*. 2007;13:254–261.
8. Brenner DA, Paik Y-H, Schnabl B. Role of gut microbiota in liver disease. *J Clin Gastroenterol*. 2015;49(suppl):S25–S27.
9. Qamar AA. Probiotics in nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, and cirrhosis. *J Clin Gastroenterol*. 2015;49(suppl):S28–S32.
10. Mittal VV, Sharma BC, Sharma P, et al. A randomized controlled trial comparing lactulose, probiotics, and


*Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.*


Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

L-ornithine L-aspartate in treatment of minimal hepatic encephalopathy. *Eur J Gastroenterol Hepatol*. 2011;23: 725–732.
11. Agrawal A, Sharma BC, Sharma P, et al. Secondary prophylaxis of hepatic encephalopathy in cirrhosis: an open-label randomized controlled trial of lactulose, probiotics and no therapy. *Am J Gastroenterol*. 2012;107:1043–1050.
12. Shukla S, Shukla A, Mehboob S, et al. Meta-analysis: the effects of gut flora modulation using prebiotics, probiotics and synbiotics on minimal hepatic encephalopathy. *Alimen Pharmacol Ther*. 2011;33:662–671.
13. Aller R, De Luis DA, Izaola O, et al. Effect of a probiotics on liver aminotransferases in nonalcoholic fatty liver disease patients: a double blind randomized clinical trial. *Eur Rev Med Pharmacol Sci*. 2011;15:1090–1095.
14. Loguercio C, Federico A, Tuccillo C, et al. Beneficial effects of a probiotics VSL#3 on parameters of liver dysfunction in chronic liver diseases. *J Clin Gastroenterol*. 2005;39:540–543.
15. Wai-Sun Wong V, Lai-Hung Wong G, Mei-Ling Chim A, et al. Treatment of nonalcoholic steatohepatitis with probiotics. A proof-of-concept study. *Ann Hepatol*. 2013;12:256–262.
16. Malaguarnera M, Vacane M, Antic T, et al. *Bifidobacterium longum* with fructo-oligosaccharides in patients with non-alcoholic steatohepatitis. *Dig Dis Sci*. 2012;57:545–553.
17. Miloh T. Probiotics in pediatric liver disease. *J Clin Gastroenterol*. 2015;49(suppl):S33–S36.
18. Guarino A, Guandalini S, Lo Vecchio A. Probiotics for prevention and treatment of diarrhea. *J Clin Gastroenterol*. 2015;49(suppl):S37–S45.
19. Guslandi M. Role of probiotics in Crohn's disease and in pouchitis. *J Clin Gastroenterol*. 2015;49(suppl):S46–S49.
20. Chibbar R, Dieleman LA. Probiotics in the management of ulcerative colitis. *J Clin Gastroenterol*. 2015;49(suppl):S50–S55.
21. Ringel Y, Ringel-Kulka T. The intestinal microbiota and irritable bowel syndrome. *J Clin Gastroenterol*. 2015; 49(suppl):S56–S59.
22. Quigley EMM. Probiotics in irritable bowel syndrome; the science and the evidence. *J Clin Gastroenterol*. 2015;49(suppl):S60–S64.
23. Brandt LJ. Fecal microbiota transplant; respice, adspice, prospice. *J Clin Gastroenterol*. 2015;49(suppl):S65–S68.
24. Louie T, Cannon K, O'grady H, et al. Fecal microbiome transplantation (FMT) via oral fecal microbial capsules for recurrent *Clostridium difficile* infection (rCDI). Presented at ID week, 201389. October 3, 2013. Los Angeles, CA.
25. Youngster I, Russell GH, Pindar C, et al. Oral, capsulized, frozen fecal microbiota transplantation for relapsing *Clostridium difficile* infection. *JAMA*. 2014;31:1772–1778.
26. Floch MH, Walker WA, Madsen K, et al. Recommendations for probiotic use—2011 update. *J Clin Gastroenterol*. 2011;45: S168–S171.
27. Guarino A, Ashkenazi S, Gendrel D, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/ European Society for Pediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe update 2014. *J Pediatr Gastroenterol Nutr*. 2014;59:132–152.
28. Szajewska H, Guarino A, Hojsak I, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. Use of probiotics for management of acute gastroenteritis: a position paper by the ESPGHAN Working Group for Probiotics and Prebiotics. *J Pediatr Gastroenterol Nutr*. 2014;58:531–539.
29. Szajewska HJ, Skórka A, Dylag M. Meta-analysis: *Saccharomyces boulardii* for treating acute diarrhea in children. *Aliment Pharmacol Ther*. 2007;25:257–264.
30. Szajewska H, Urbańska M, Chmielewska A, et al. Meta-analysis: *Lactobacillus reuteri* strain DSM 17938 (and the original strain ATCC 55730) for treating acute gastroenteritis in children. *Benef Microbes*. 2014;5:285–293.
31. Surawicz CM. Role of probiotics in antibiotic associated diarrhea, *Clostridium difficile* associated diarrhea and recurrent *Clostridium difficile* diarrhea. *J Clin Gastroenterol*. 2008;42:S64–S70.
32. Doron S, Hibberd P, Gorbach SL. Probiotics for prevention of antibiotic-associated diarrhea. *J Clin Gastroenterol*. 2008;42: S58–S63.
33. Hickson M, D'Souza AL, Muthu N, et al. Use of probiotic *Lactobacillus* preparation to prevent diarrhea associated with antibiotics: randomized double blind placebo controlled trial. *BMJ*. 2007;355:80.
34. Na X, Kelly C. Probiotics in *Clostridium difficile* infection. *J Clin Gastroenterol*. 2011;45:S154–S158.
35. Evidence-based medicine. Available at: http://en.wikipedia.org/wiki/Evidence-based_medicine. Accessed June 26, 2011.
36. Brandt LJ, Reddy SS. Fecal microbiotic transplantation for recurrent *Clostridium difficile* infection. *J Clin Gastroenterol*. 2011;45:S159–S167.
37. Katz JA. Probiotics for the prevention of antibiotic-associated diarrhea and *Clostridium difficile* diarrhea. *J Clin Gastroenterol*. 2006;40:249–255.
38. Gionchetti P, Rizzello F, Venturi A, et al. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. *Gastroenterology*. 2000;119:305–309.
39. Gionchetti P, Rizzello F, Helwig U, et al. Prophylactis of pouchitis onset with probiotic therapy: a double-blind, placebo-controlled trial. *Gastroenterology*. 2003;124:1202–1209.
40. Mimura T, Rizzello F, Helwig U, et al. Once-daily high-dose probiotic therapy (VSL#3) for maintaining remission in recurrent or refractory pouchitis. *Gut*. 2004;53:108–114.
41. Gionchetti P, Rizzello F, Morselli C, et al. High-dose probiotics for the treatment of active pouchitis. *Dis Colon Rectum*. 2007;50:2075–2084.
42. Rembacken FJ, Snelling AM, Hawkey PM, et al. Nonpathogenic *Escherichia coli* versus mesalazine for the treatment of ulcerative colitis: a randomized trial. *Lancet*. 1999;354:635–639.
43. Bibiloni R, Fedorak RN, Tannock GW, et al. VSL#3 probiotic-mixture induces remission in patients with active ulcerative colitis. *Am J Gastroenterol*. 2005;100:1539–1546.
44. Miele E, Pascarella F, Giannetti E, et al. Effect of a probiotic preparation (VSL#3) on induction and maintenance of remission in children with ulcerative colitis. *Am J Gastroenterol*. 2009;104:437–443.
45. Kruis W, Fric P, Pokrotnieks J, et al. Maintaining remission of ulcerative colitis with the probiotic *Escherichia coli* Nissle 1917 is as effective as with standard mesalazine. *Gut*. 2004;53:1617–1623.
46. Malchow HA. Crohn's disease and *Escherichia coli*: a new approach in therapy to maintain remission of colonic Crohn's disease. *J Clin Gastroenterol*. 1997;25:653–658.
47. Guslandi M, Mezzi G, Sorghi M, et al. *Saccharomyces boulardii* in maintenance treatment of Crohn's disease. *Dig Dis Sci*. 2000;45:1462–1464.
48. Gupta P, Andrew H, Kirschner BS, et al. Is *Lactobacillus* GG helpful in children with Crohn's disease? Results of a preliminary open-label study. *J Pediatr Gastroenterol Nutr*. 2000;31:453–457.
49. 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;101:1581–1590.
50. O'Mahony L, McCarthy J, Kelly P, et al. *Lactobacillus* and *Bifidobacterium* in irritable bowel syndrome (IB): symptom responses and relationship to cytokine profiles. *Gastroenterology*. 2005;128:541–551.
51. Kim JH, Camilleri M, McKenzie S, et al. A randomized controlled trial of a probiotic, VSL#3 on gut transit and symptoms in diarrhea-predominant IBS. *Aliment Pharmacol Ther*. 2003;17:895–904.
52. Kim JH, Vazquez Roque MI, Camilleri M, et al. A randomized controlled trial of probiotic combination VSL#3 and placebo in IBS with bloating. *Neurogastroenterol Motil*. 2005;17:687–696.
53. Guandalini S, Magazzu G, Chiaro A, et al. VSL#3 improves symptoms in children with irritable bowel syndrome: an


*Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.*

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

international, randomized, placebo-controlled, double-blinded, cross-over study. *J Pediatr Gastroenterol Nutr*. 2010;51:24–30.
54. Guyonnet D, Chassany O, Ducrotte P, et al. Effect of a fermented milk containing *Bifidobacterium animalis* DN-172 010 on the health-related quality of life and symptoms in irritable bowel syndrome in adults in primary care: a multicentre, randomized double-blind, controlled trial. *Aliment Pharmacol Ther*. 2007;26:475–486.
55. Niedzielin K, Kordecki H, Birkenfeld B, et al. A controlled, double-blind, randomized study on the efficacy of *Lactobacillus plantarum* 299V in patients with irritable bowel syndrome. *Eur J Gastroenterol Hepatol*. 2001;13:1143–1147.
56. Ganguli K, Walker WA. Probiotics in the prevention of necrotizing enterocolitis. *J Clin Gastroenterol*. 2011;45: S133–S138.
57. Lin HC, Chyong-Hsin H, Hsiu-Lin C, et al. Oral probiotics prevent necrotizing enterocolitis in very low birth rate preterm infants: a multicenter, randomized, controlled trial. *Pediatrics*. 2008;122:693–700.
58. Isolauri E, Joensuu J, Suomalainen H, et al. Improved immunogenicity of oral DxRRV reassortant rotavirus vaccine by *Lactobacillus casei* GG. *Vaccine*. 1995;13:310–312.
59. Isolauri E, Salminen S. Probiotics: use in allergic disorders. *J Clin Gastroenterol*. 2008;42:S91–S96.
60. Delia P, Sansotta G, Donato V, et al. Prevention of radiation-induced diarrhea with the use of VLS#3, a new high-potency probiotic preparation. *Am J Gastroenterol*. 2002;97: 2150–2152.
61. Salminen E, Eloman I, Minkkinen J, et al. Preservation of intestinal integrity during radiotherapy using live *Lactobacillus acidophilus* cultures. *Clin Radiol*. 1988;39:435–437.
62. Hilton F, Isenberg HD, Alperstein P, et al. Ingestion of yogurt containing *Lactobacillus acidophilus* as prophylaxis for candida vaginitis. *Am Intern Med*. 1992;116:353–357.
63. Anukam K, Osazuwa E, Ahonkhai I, et al. Augmentation of antimicrobial metronidazole therapy of bacterial vaginosis with oral probiotic *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14: randomized, double-blind, placebo controlled trial. *Microbes Infect*. 2006;8:2772–2776.
64. Anukam KC, Osazuwu E, Osemen GI, et al. Clinical study comparing probiotic *Lactobacillus* GR-1 and RC-14 with metronidazole vaginal gel to treat symptomatic bacterial vaginosis. *Microbes Infect*. 2006;8:2772–2776.

*Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.*


Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.