Recommendations for Probiotic Use—2015 Update

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Recommendations for Probiotic Use—2015 Update

Proceedings and Consensus Opinion

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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

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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

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.

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.

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