

## Recommendations for Probiotic Use—2011 Update

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**Abstract:** This study describes the consensus opinion of the participants of the third Yale Workshop on probiotic use. There were 10 experts participating. The recommendations update those of the first 2 meetings that were published in 2005 and 2008. The workshop presentations and papers in this supplement relate to the involvement of normal microbiota involved in intestinal microecology, how the microbes interact with the intestine to affect our immunologic responses, the stability and natural history of probiotic organisms, and the role of the intestinal microbatome with regard to affecting cardiac risk factors and obesity. Recommendations for the use of probiotics in necrotizing enterocolitis, childhood diarrhea, inflammatory bowel disease, irritable bowel syndrome, and *Clostridium difficile* diarrhea are reviewed. As in previous publications, the recommendations are given as A, B, or C ratings. The recent positive experiences with bacteriotherapy (fecal microbiome transplant) are also discussed in detail and a positive recommendation is made for use in severe resistant *C. difficile* diarrhea.

**Key Words:** probiotics, recommendations, diarrhea

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The first Yale Workshop on Probiotics was convened in 2004. The clinical use of probiotics had gained worldwide attention of patients and health care delivery personnel, but although there was a growing literature on clinical trials, there were few clinical recommendations. Hence, we gathered thought leaders and investigators in the field and published the first workshop recommendations in 2005.<sup>1</sup> We held the second workshop with some of the original contributors but added others to broaden our view. The results of the second workshop were published in 2008.<sup>2</sup>

This paper<sup>3</sup> represents the work of 10 experts of the third Yale Workshop held in New Haven in April 2011.

Dr Walker and I designed this program in an effort to include the newer concepts on the use of probiotics to maintain health. The work presented explores probiotic interaction with the immune system.<sup>4</sup> The importance of these interactions to overall host health is not yet fully understood. Questions such as how much do supplemental probiotic organisms contribute to immune status compared with the natural physiologic effects of the microbiome?, can a single organism have an important impact?, or are multiple organisms needed? are discussed.<sup>5</sup>

We also included in this workshop a discussion of the effects of colonic fermentation on health<sup>6</sup> and how it may affect cardiac risk factors. The early concepts of how the microbiome may affect obesity also are covered.<sup>7</sup> The supplement includes detailed articles on all of these factors.

We reviewed the recommendations in diseases made in 2005 and 2008 and updated them. Updates on inflammatory bowel disease,<sup>8</sup> the irritable bowel syndrome,<sup>9</sup> infectious diarrhea,<sup>10</sup> and *Clostridium difficile* infection are given.<sup>11</sup>

The user should be aware that some of the recommendations were made by the investigators of the first 2 workshops. All authors have cleared this publication, but there is still controversy on some of the diseases of the designations of an A, B, or C rating.

We have continued to use the rating system first used in our 2005 report. This is an arbitrary system. As noted in encyclopedic references,<sup>12</sup> there are many rating systems, and in clinical evidence-based medicine, they are frequently controversial. We used “A” recommendation to mean strong, positive studies in the literature. “B” recommendation is based on positive-controlled studies, but the presence of some negative studies that did not support the primary outcome. “C” recommendation is based on some positive studies, but

**TABLE 1.** Recommendations for Probiotic Use—Update 2011

Clinical Condition	Effectiveness	Specific Strain of Organism and Strain References	Analysis References
<b>Diarrhea</b>			
Infectious childhood—treatment	A	<i>Saccharomyces boulardii</i> , <sup>15</sup> LGG, <sup>16</sup> <i>Lactobacillus reuteri</i> SD2112 <sup>17</sup>	15–18
Prevention of infection	B	<i>S. boulardii</i> , <sup>15</sup> LGG <sup>16</sup>	15,16,18
Prevention of AAD	A	<i>S. boulardii</i> , <sup>19</sup> LGG, <sup>20</sup> combination of <i>Lactobacillus casei</i> DN114 G01, <i>Lactobacillus bulgaricus</i> , snf <i>Saccharomyces thermophilus</i> <sup>21</sup>	19–21
Prevention of recurrent CDAD	B/C	<i>S. boulardii</i> , <sup>11</sup> LGG, <sup>22</sup> bacteriotherapy <sup>14</sup>	11,12,14,22
Prevention of CDAD	B/C	LGG, <sup>11</sup> <i>S. boulardii</i> <sup>22</sup>	11,22
<b>IBD</b>			
Pouchitis			
Preventing and maintaining remission	A	VSL#3 <sup>23–25</sup>	23–25
Induce remission	C	VSL#3 <sup>26</sup>	26
Ulcerative colitis			
Inducing remission	B	<i>Escherichia coli</i> Nissle <sup>27</sup> , VSL#3 <sup>28</sup>	27–29
Maintenance	A	<i>E. coli</i> Nissle, <sup>30</sup> VSL#3 <sup>29</sup>	28–30
Crohn’s	C	<i>E. coli</i> Nissle, <sup>31</sup> <i>S. boulardii</i> , <sup>32</sup> LGG <sup>33</sup>	31–33
<b>IBS</b>			
	B	<i>Bifidobacterium infantis</i> B5624, <sup>34,35</sup> VSL#3 <sup>34–37,48</sup>	34–37,48,†
	C	<i>Bifidobacterium animalis</i> <sup>38</sup> <i>Lactobacillus plantarum</i> 299V <sup>39</sup>	38 39
<b>Necrotizing Enterocolitis</b>	B	<i>Lactobacillus acidophilus</i> NCDO1748 <sup>13</sup> and <i>Bifidobacterium bifidum</i> NCDO1453 <sup>47</sup>	13,47
<b>Recommendations From 2008*</b>			
<b>Immune response</b>	A	LGG, <i>Lactobacillus acidophilus</i> LAFT1, <i>Lactobacillus plantarum</i> , <i>Bifidobacterium lactis</i> , <i>Lactobacillus johnsonii</i>	40,41
<b>Allergy</b>			
Atopic eczema associated with cow’s milk allergy			
Treatment	A	LGG, <i>Bifidobacterium lactis</i> <sup>41</sup>	41
Prevention	A	LGG, <i>B. lactis</i> <sup>41</sup>	41
<b>Radiation enteritis</b>	C	VSL#3, <sup>42</sup> <i>L. acidophilus</i> <sup>43</sup>	42,43
<b>Vaginosis and vaginitis</b>	C	<i>L. acidophilus</i> , <sup>44</sup> <i>Lactobacillus rhamnosus</i> GR-1, <sup>45</sup> <i>L. reuteri</i> RC14 <sup>46</sup>	44–46

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

†Reference<sup>48</sup> 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.

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

clearly inadequate amount of work to establish certainty. Where we thought experience was inadequate or there were too few studies for a reasonable conclusion, we made no recommendation. This system is similar to those used in evidence-based writings.

Table 1 is an update of that published in the last recommendations.<sup>2</sup> This table includes more clinical conditions and makes recommendations that would affect the healthy population. Some recommendations not discussed at this workshop but those made in 2008 are included in the table. The recommendations for *C. Difficile*-associated diarrhea were downgraded from B to B/C by the information analyzed by Na and Kelly<sup>11</sup> as compared with that discussed in 2005<sup>1</sup> and 2008.<sup>2</sup> The first recommendation was made for necrotizing enterocolitis particularly because of the published papers on the subject from

Taiwan in 2008 which were very encouraging and the strong meta-analysis literature. However, it must be stressed that if probiotics are used, the strains used in a specific reference should be followed.<sup>13,47</sup> Finally, as there is now clinical evidence that transplanting the entire intestinal microbiota is beneficial in severe relapsing *C. difficile* diarrhea, we have presented that information as part of our recommendations.<sup>14</sup>

We would like to emphasize that these recommendations are based on the literature that is available at this time. It must also be stressed that these recommendations are strain specific. Strains are listed in the table for most, but when not listed, we provide references that can be consulted for the strain. Anyone using these recommendations must refer to the reference and the specific strain used in referenced studies.

There are now many published meta-analyses and ratings published and those are referred to in the articles in this supplement. We hope that this review will be helpful to clinicians seeking clinical advice on the use of probiotics.

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