Abstract: Recommendations for the clinical use of probiotics were published after a Yale University Workshop in 2005. A similar workshop was held in 2007, and the recommendations were updated and extended into other areas. The recommendations are graded into an “A,” “B,” “C” or no category based on the expert’s opinion and review by the workshop participants. An “A” recommendation is made for acute childhood diarrhea, prevention of antibiotic-associated diarrhea, preventing and maintaining remission in pouchitis, and in an immune response for the treatment and prevention of atopic eczema associated with cow’s milk allergy. The group maintained several “B” recommendations in other areas of treating inflammatory bowel disease and irritable bowel syndrome. Although there are significant studies in the “B” group, most “B” recommendations did not reach an “A” level because of some negative studies or a limited number of studies. Many reports in the “C” recommendations were significant but fell short of receiving stronger ratings because of the size of reported patient studies, and also the factors that limited categories to the “B” rating.

Key Words: probiotics, recommendations, diarrhea, antibiotic-associated diarrhea, pouchitis, immune response, atopic eczema, inflammatory bowel disease, irritable bowel syndrome

Recommendations for Probiotic Use—2008

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These recommendations are made on evidence presented at the Advances in Clinical Use of Probiotics Workshop that was held at Yale University on November 16, 2007. This is the second workshop on this topic. The first workshop resulted in the publication of the 2005 Recommendations for Probiotic Use.1 The recommendations presented here are an update of the 2005 recommendations and an extension into other areas of clinical use.

All of the authors of this manuscript had an opportunity to review these recommendations, which are a result of an open discussion that occurred at the workshop, and the manuscripts that are presented in this supplement.

These recommendations carry with them certain caveats:
1. Specific recommendations made for clinical use are referenced to a manuscript that describes the probiotic used, the dose and the probiotic strain or strains used, and the vehicle in which it was delivered. We caution that the recommendations are based on those referenced results and cannot be extrapolated to the use of other products. The references are specific. Clinicians may want to use a similar probiotic but should do that with the understanding that the reported result is based on the probiotic and the way it was used as cited in the reference. It is emphasized that the probiotic upon which a recommendation is based are for specific strains of organisms and specific products used in the referenced work.
2. The dose and method of administration are important. If a recommendation is to be followed, it is for the dose that was used in the reference.
3. On the basis of the most recent literature, it is strongly recommended that probiotics be used with caution and appropriate monitoring in immunocompromised patients.

USE IN SPECIFIC CONDITIONS

Table 1 outlines guidelines for probiotic use. It is updated in this manuscript from the previous report.1 The recommendations for these guidelines are based on the discussions at the workshop and the literature.

An “A” recommendation is based on strong, positive, well-conducted, controlled studies in the primary literature, not abstract form.
A “B” recommendation is based on positive, controlled studies but the presence of some negative studies. A “C” recommendation is based on some positive studies but clearly inadequate amount of work to establish the certainty of “A” or “B.”

**DIARRHEA**

**Treatment of Nonantibiotic-associated Diarrhea of Children and Adults**

The recommendations at this workshop were essentially the same as the previous recommendations. Probiotics are helpful in acute childhood diarrhea and given an “A” recommendation.

The organisms that seem to be effective, considering the treatments throughout the world, are referenced—Saccharomyces boulardii, Lactobacillus GG (LGG), Lactobacillus reuteri and a variety of mixtures, including Lactobacillus acidophilus. The references are for the doses and the specific strains used at the onset of diarrhea. There is an approximately 24 to 30 hours reduction in the illness.

Only a “B” recommendation is given for prevention of sporadic, infectious diarrhea. In fact, although all probiotics tested were found to be completely safe, the evidence of their efficacy in preventing diarrheal episodes in infants and children attending daycare centers or being hospitalized for reasons other than diarrhea is only modest statistically significant for some strains only, and in any case of questionable clinical importance. However, this is most definitely an area worth further exploration.

**Antibiotic-associated Diarrhea**

Antibiotic-associated Diarrhea (not due to *Clostridium difficile*)

An “A” recommendation is given for prevention in ambulatory and hospitalized adult patients. LGG and *S. boulardii* are effective. There are good studies for both inpatients and outpatients. A recent meta-analysis on 10 randomized-controlled clinical trials confirms the efficacy of LGG and *S. boulardii* in the prevention of antibiotic-associated diarrhea in children. One recent study did show a combination of *L. casei, L. bulgaricus, and S. thermophilus* was effective in a drink given twice per day.

C. *difficile*-associated Diarrhea

There are conflicting opinions on whether probiotics have any role in prevention of *C. difficile*-associated diarrhea (CDAD) or treatment of initial or severe episodes of CDAD.

The specific initial treatment of *C. difficile* diarrhea is one of the antibiotic treatments of the *C. difficile*. As many as one-third of the patients will relapse after treatment and persistent *C. difficile* can be demonstrated. In these cases, probiotics become important as an adjuvant in the treatment. For this purpose, either *S. boulardii* or LGG are effective.
The evidence on using probiotics for prevention or recurrent CDAD is debated. However, meta-analysis does reveal positive data using either LGG or *S. boulardii*. Therefore, it is given a “B” recommendation for prevention and as adjuvant therapy. It was further noted in the presentations that fecal transplant bacteria therapy has anecdotally and in small studies reported as effective in many centers. No recommendation is made at this time for fecal transplant, but it must be noted that several centers have reported it as effective in resistant cases.

**INFLAMMATORY BOWEL DISEASE POUCHITIS**

**Pouchitis**

**Maintenance of Remission**

An “A” recommendation continues for the maintenance of remission of pouchitis in ileal-pouch-anal-anastomosis, either after induction of remission with antibiotic therapy or immediately after surgical formation of the pouch. VSL#3 is the probiotic mixture that has been reported as effective in the literature. Use and dosage are as recommended in the specific references.

**Induction of Remission**

There is a level “C” recommendation for induction of remission of pouchitis given a recently published open-label study that demonstrated that high dose VLS#3 was able to induce remission of active pouchitis.

**Ulcerative Colitis**

**Maintenance of Remission**

The workshop panel felt that there was “C” evidence for maintenance of remission using *Escherichia coli* Nissle, in that the 2 large randomized-controlled trials have demonstrated that *E. coli* Nissle had similar efficacy to that of mesalamine. Because of the 2 positive trials, this can be considered as a “B” but many felt there were not strong enough published data in this controversial area.

**Induction of Remission**

For induction of remission, the workshop panel agreed that a “C” recommendation remains because the trials were limited to open-label studies. However, there is accumulating evidence suggestive that it maybe helpful. Both *E. coli* Nissle and VSL#3 hold promise as being helpful in acute ulcerative colitis, but random-controlled trials in larger number of patients are still needed. *E. coli* Nissle has been used both in induction and maintenance of remission, whereas VSL#3 seemed effective in inducing remission, as an adjuvant therapy, and in maintaining remission.

**Crohn’s Disease**

The recommendation for this remains at a “C” level for both induction of remission and maintenance of remission. Results are variable, studies are small, mostly open label, and there are not enough studies or with large enough number of patients to make a definite recommendation.

*E. coli* Nissle, *S. boulardii*, and LGG have been used with variable results.

**IRRITABLE BOWEL SYNDROME**

Because of the high incidence of this syndrome, there is a great deal of interest. There are mixed opinions of whether to leave this at a “C” level, because there are some promising results that demonstrate a decrease in symptoms. On the basis of expert opinion, we have listed it as both “B” and “C” for different probiotics. *Bifidobacterium infantis* and *Bifidobacterium animalis* have shown to relieve symptoms in most recent studies. Older studies used *Lactobacillus plantarum* with some success but have not been repeated. Only *B. infantis* has been raised to a “B” level based on 2 large, random, controlled trials.

**IMMUNE RESPONSE AND ALLERGY**

**Immune Response**

The panel now feels that they can give this an “A” recommendation. The evidence has accumulated and substantiated that the immune response is definitely affected by the administration of probiotics.

Furthermore, it is now accepted in many areas of the world that probiotics are helpful in the treatment of childhood allergy and eczema. The workshop panel discussed allergy for the first time. The all encompassing data were presented. We now feel we can make an “A” recommendation for the use of specific probiotics, particularly the strains of LGG and *Bifidobacterium lactis*, in infants and children for the treatment of allergic disorders with intestinal involvement, such as atopic eczema associated with cow’s milk allergy and their prevention.

**OTHER DISEASES**

**Necrotizing Enterocolitis**

This was reviewed in detail. There is not enough information to make a recommendation. Studies have been small and used different probiotics in different populations. However, the use of probiotics to prevent enterocolitis is promising, and more information should be forthcoming and should enable a recommendation in future years.

**Radiation Enteritis**

A “C” recommendation is made because there are limited studies. However, the data in these studies are impressive, but the number of subjects studied is small. More data are needed before the recommendation can be upgraded.

VSL#3 has been used effectively, and also the strains of *L. acidophilus* in those studies.
**Vaginitis and Vaginosis**

This was not specifically addressed at the conference, but probiotics seem promising in the treatment of vaginitis and vaginosis. The previously assigned category “C” recommendation stands, although the 2 recent controlled trials from Africa are impressive.

The organisms used have been LGG,\(^{53}\) *L. reuteri*,\(^{53,54}\) and *L. acidophilus*.\(^ {55}\)

**PREVENTION OF DISEASE IN HEALTH MAINTENANCE**

In many societies of the world, probiotics and yogurts as foods are used to maintain health.\(^ {65}\) The feeling is that this is such a broad area of study that additional studies for the different end points (eg, duration of colds or absences from work) are needed so that specific recommendations can be made.

A variety of studies have been conducted with probiotics which suggest that consuming them may help keep people healthy.\(^ {56}\) *L. reuteri* ATCC 55730 was shown to reduce absences from work or daycare, crying time in colicky babies, and episodes of fever and diarrhea in infants with childcare. *Lactobacillus casei* DN114-001 and LGG also improved resistance to illness in children in daycare settings. A combination probiotic (*Bifidobacterium longum, Bifidobacterium bifidum, Lactobacillus gasseri*) tested in healthy adults showed a reduction in duration, but not incidence, of colds. The likely mechanisms for this effect include enhancement of immune function and direct inhibition of pathogens. Such findings suggest that probiotics might be of value for incorporation into the daily diet of healthy people for the purpose of staying healthy. However, such a recommendation is more of a dietary recommendation than a clinical one. This subject is complex and has many ramifications that the group felt prevented making a specific clinical recommendation at this time.\(^ {65,66}\)

**SUMMARY**

Uses of probiotic organisms are promising in maintaining health and treating disease in humans. Table 1 outlines our recommendations for their use. Each indication is referenced. The reference should be consulted when a probiotic is prescribed. The evidence reveals they are indicated in treatment of acute childhood diarrhea, prevention of antibiotic-associated diarrhea, pouchitis, to obtain an immune response, and in atopic dermatitis. Evidence is rapidly accumulating that they maybe helpful in other disorders such as treatment of *C. difficile*-associated colitis, radiation enteritis, ulcerative colitis, and irritable bowel syndrome. Using probiotics for other indications including maintenance in health need to be reevaluated in the next few years. There is an urgent need for improvements in the quality of clinical trials to evaluate the safety and efficacy of specific probiotics before recommendations can be upgraded.

**REFERENCES**


