CLINICAL INQUIRY

Probiotics for the Prevention of Antibiotic-Associated Diarrhea

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Clinical Question

Do probiotics reduce the risk of Antibiotic-Associated Diarrhea (AAD) in adult patients?

Evidence-Based Answer

Probiotics reduce the risk of developing antibiotic-associated diarrhea (Strength of Recommendation (SOR) A). (See appendix for the Strength of Recommendation taxomony.) *Saccharomyces boulardii* and *Lactobacillus* species have been shown to reduce the risk of antibiotic-associated diarrhea (SOR A). Probiotics should be recommended for the prevention of antibiotic-associated diarrhea (SOR C). However, the duration and dosage for effective treatment have not been established.

Methodology

A tertiary review of existing systematic reviews was conducted. PubMed was searched for articles unrestricted by language from inception to 6/11/2013. Terms were searched as text words and included: probiotics, diarrhea, and meta-analysis. Abstracts of the 77 results were reviewed to eliminate any that did not pertain to prevention of antibiotic-associated diarrhea in adults, resulting in 26 articles. The plethora of recent randomized controlled trials and meta-analyses allowed a focus on the five relevant meta-analyses published in the past five years that included at least 10 randomized controlled trials (RCTs) each.[1-5]

Data were included on all types of probiotics used in adults (at least 16 years old). The meta-analyses used both inpatient and outpatient settings and defined AAD in various ways. Where meta-analyses included minors or treatment studies, only the subset of data relevant to prevention in adults was examined.

Evidence Summary

The occurrence of AAD ranges from 5 to 30% in outpatient use and has been reported as high as 39% in hospitalized patients,[6] leading to significant healthcare costs due to associated morbidity. AAD is also a reason that many patients are noncompliant with antibiotic use. Therefore, finding a way to reduce AAD has become of increasing interest, particularly with the use of probiotics. Probiotics have been defined as "live microorganisms, which when administered in adequate amounts, confer a health benefit on the host".[7] The use of probiotics in

the prevention of AAD has been studied widely and overall has positive results in reducing AAD.

Probiotics reduce the risk of developing AAD. Hempel et al.[2] performed the most exhaustive meta-analysis on randomized control trials (RCTs) of probiotics for the prevention of AAD. Their subgroup analysis of 14 RCTs limited to participants aged 18 to 65 years demonstrated that probiotic administration was associated with reduction of AAD by 46% (RR = 0.54, 95% CI: 0.34 - 0.85, NNT = 13).[3] A pooled analysis of all 45 study arms meeting our inclusion criteria gave similar results (RR = 0.59; 95% CI: 0.53 - 0.67, NNT = 15). The results suggested that probiotics are efficacious in the prevention of AAD. Though the majority of studies focused on *Lactobacillus*, many strains and combinations of probiotics were used and reporting often was insufficient to determine the exact regimen used in a particular study. Importantly, regardless of subgroup analysis, the results remained statistically significant. This meta-analysis was unable to identify which strains or doses were truly beneficial.

A recent Cochrane meta-analysis focused on AAD studies that included a measure of *C. difficile*.[1] The subset of 19 studies in adults with AAD showed a 37% reduction in risk (RR = 0.63; 95% CI: 0.51 - 0.76). A risk reduction of 64% was reported in the 19 studies in adults with *C. difficile*-associated diarrhea (RR = 0.36, 95% CI: 0.24 - 0.52).

S. boulardii and *Lactobacillus* reduce the risk of developing AAD. Some meta-analyses have looked at RCTs that specifically evaluated the effect of *S. boulardii* and *Lactobacillus species* on AAD.[2-5] Overall, the results consistently have shown a significant reduction in AAD with the use of each of these probiotics.

McFarland's meta-analysis included 10 RCTs comparing *S. boulardii* to placebo and found a significant protective effect against AAD with number needed to treat being 10.2 (pooled RR = 0.47, 95% CI: 0.35 - 0.63, $p < 0.0001$, NNT = 10.2).[5]

Two meta-analyses included 12 RCTs (8 overlapping) using *Lactobacillus* species only. Pooled analysis of each showed that there was a 34% reduction in risk of AAD.[2,3] Overall, the trials showed a benefit to the use of *S. boulardii* or *Lactobacillus* in the reduction of AAD.

Probiotics should be used for the prevention of AAD. The use of probiotics repeatedly has demonstrated a reduction in AAD.[1-5] Hempel showed that the number needed to treat to prevent one case of AAD was only 13.[2] Furthermore, studies consistently note that adverse effects of probiotics rarely were reported.[6] Based on the available data, probiotics should be used for the prevention of AAD. However, research is inconclusive regarding the best probiotic regimen. More research is needed to determine clear recommendations including which strain or combination of strains to use, dosage, and duration of treatment. Many of the meta-analyses identified heterogeneity among probiotic regimens as a concern.

Recommendations from Others

An expert panel convened for the third time at Yale University in 2011 to evaluate the use of probiotics.[8] Their consensus was that there is grade A evidence (strong, positive studies in the literature) for prevention of AAD with *L. rhamnosus GG* and *S. Boulardii*, and the evidence for the mixture of *L. casei* DN-114 001, *L. delbrueckii* subspecies *bulgaricus*, and *S. thermophilus* is also strong. However, the Society for Healthcare Epidemiology of America (SHEA) and Infectious Diseases Society of America (IDSA) in their 2010 guidelines on *Clostridium difficile* infections have recommended that probiotics not be used for primary prevention of *C. difficile*. They also noted that reported cases of fungemia have occurred with the use of *S. boulardii* in severely ill and immunocompromised patients and advised against its use in these patients.[9]

References

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Keywords: probiotics, diarrhea, anti-bacterial agents

Appendix
(Adapted from American Family Physician*)

Strength of recommendation	*Basis for recommendation*
A	Consistent, good-quality patient-oriented evidence**
B	Inconsistent or limited-quality patient-oriented evidence**
C	Consensus, disease-oriented evidence** (usual practice, expert opinion, or case series for studies of diagnosis, treatment, prevention, or screening)

*http://www.aafp.org/dam/AAFP/documents/journals/afp/sortdef07.pdf

**Patient-oriented evidence measures outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life.

Disease-oriented evidence measures intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes (e.g., blood pressure, blood chemistry, physiologic function, pathologic findings).