**EDITORIAL COMMENTARY**

**Saccharomyces cerevisiae Fungemia: An Adverse Effect of Saccharomyces boulardii Probiotic Administration**

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(See the article by Muñoz et al. on pages 1625–34)

A probiotic can be defined as a live, non-pathogenic microbial supplement that exerts a positive influence on the health or physiology of the host [1, 2]. Probiotics consist of either bacteria, especially lactic acid bacteria, or yeast. Probiotics have mainly been used for gastrointestinal and vaginal diseases [3].

The effects of probiotics are thought to be related to direct enzymatic effects or to a modulation of the endogenous flora or of the immune system [4]. Efficacy of probiotics in persons with enzymatic defects is now well accepted. Lactase from lactic acid–producing bacteria contained in yoghurt helps to digest lactose in subjects with lactose intolerance and in those with short-bowel syndrome [1]. *Saccharomyces cerevisiae* expresses significant sucrase and some isomaltase activity but no lactase activity, and it has been proposed to improve malabsorption in patients with sucrase-isomaltase deficiency who intentionally or unintentionally consume sucrose [5].

Antibiotic-induced microbial imbalance is a common cause of diarrhea and, in severe cases, of pseudomembranous colitis. Attempts have been made to determine whether the administration of probiotics would prevent or treat antibiotic-associated diarrhea. Several randomized trials successfully demonstrated a reduced risk of antibiotic-associated diarrhea when *Lactobacillus acidophilus* plus *Lactobacillus bulgaricus, Lactobacillus rhamnosus* GG, *Enterococcus faecium* SF68 (a lactic acid–producing strain), *Bifidobacterium longum* (with or without *Lactobacillus* species), or *Saccharomyces boulardii* were administered concomitantly with the antibiotic [1]. A meta-analysis was recently conducted by D’Souza et al. [2] to evaluate the efficacy of probiotics for prevention and treatment of antibiotic-associated diarrhea. Nine double-blind, placebo-controlled trials were relevant for this analysis. Four of the trials used *S. boulardii*, and 5 used lactobacilli or *E. faecium* SF68. The OR for the pooled data from the 9 studies (0.37; 95% CI, 0.26–0.52) was in favor of active treatment over placebo for the prevention of antibiotic-associated diarrhea. In a separate analysis, the yeast and the nonyeast trials showed a similar beneficial effect (OR, 0.39 and 0.34, respectively; 95% CI, 0.25–0.62 and 0.19–0.61, respectively).

In addition to these studies, a double-blind, randomized, placebo-controlled study of 124 patients also demonstrated that the combination of antibiotics (vancomycin and/or metronidazole) and *S. boulardii* more efficaciously prevented the recurrence of *Clostridium difficile*-associated diseases than did antibiotics plus placebo (26% vs. 45%) [6]. A follow-up study performed to standardize the dose and duration of antimicrobial therapy showed that the combination of *S. boulardii* and high-dose vancomycin (2 g/day) reduced the frequency of recurrences, but *S. boulardii* therapy had no effect when combined with low doses of vancomycin (500 mg/day) or metronidazole (1 g/day) [7].

Interestingly, *S. boulardii* produces a protease that can digest toxins A and B of *C. difficile* [8]. This proteolytic activity of *S. boulardii* may explain the protective effect against *C. difficile*–associated diarrhea. Moreover, the *S. boulardii* protease diminishes the ability of toxins A and B to bind to human colonic brush border membrane receptor [9].

Several studies suggest the efficacy of various species of *Lactobacillus* as well as of *E. faecium* SF68, *Bifidobacterium bifidum* and *Streptococcus thermophilus*, and *S. boulardii* for preventive or curative treatment of rotavirus-associated gastroenteritis and, to a lesser extent, for the prevention of traveler’s diarrhea [1].

Finally, a limited number of animal studies and clinical trials of probiotics have shown some improvement in cases of inflammatory bowel diseases, such as Crohn...
disease, suggesting an immunomodulatory effect for probiotics [1, 10].

Probiotics are becoming increasingly available as dietary supplements, are largely used in the dairy food industry, and, in continental Europe, are regarded as medicines. S. boulardii (Ultra-Levure [Biocodex], Ultralevura [Bristol-Myers Squibb], and Codex [Zambon Farmaceutici]) is registered in several European countries and has been proposed for the treatment of several types of diarrhea, either as prophylaxis against antibiotic-associated diarrhea or as a treatment for diarrheaa in adults and children infected with C. difficile, for diarrhea in HIV-infected patients, and for acute diarrhea in children and adults. Contraindications listed for Ultra-Levure in the French labeling are hypersensitivity or intolerance to one of the constituents and presence of a central venous catheter. The latter contraindication derives from cases of S. boulardii fungemia predominantly reported in patients with central venous lines in place [11, 12]. The origin of the fungemia is thought to be either a digestive tract translocation or a contamination of the central venous line by the colonized hands of health care workers after the probiotic capsules have been opened [11].

Many cases of fungemia due to S. cerevisiae (well known as “baker’s yeast” or “brewer’s yeast”) or S. boulardii have been reported. Whether S. boulardii is different from S. cerevisiae was a matter of debate [13]; this debate is now over. Despite certain phenotypic differences, genotypic and proteomic analyses have definitively recognized S. boulardii as a member of the species S. cerevisiae [14, 15]. S. boulardii strains as obtained in France and Italy from commercially available products exert intermediate virulence, compared with virulent and avirulent strains of S. cerevisiae [16]. In several cases, the fungemia has been related to the use of the probiotic agent in the patient immediately prior to or concomitantly with the fungemia [11, 16].

In this issue, Munoz et al. [17] add 3 new cases of S. cerevisiae fungemia to the list. The originality of this publication is the demonstration that the strains were identical in all 3 patients and, furthermore, that they were identical to the strain given orally as Ultralevura to these patients before the onset of fungemia. The authors report an outbreak of 3 cases of S. cerevisiae fungemia over a 2-week period in an intensive care unit. The reason for the prescription of the probiotic was C. difficile-associated diarrhea. All 3 patients received S. boulardii from opened capsules of Ultralevura administered via nasogastric tubes. Probiotic treatment was started 7 or 8 days before the fungemia occurred. The authors reviewed the records of the 41 patients without S. cerevisiae fungemia who had been hospitalized in this intensive care unit during the same period. Only 2 of the 41 control patients had received Ultralevura, and none of the 14 patients admitted to the unit when the outbreak of infection occurred were recognized to have had positive surveillance culture results at entry into the unit. Discontinuation of the Ultralevura therapy in the unit stopped the outbreak. The authors demonstrated, by molecular typing, that the strains isolated in the 3 cases were similar to the strains cultured from an Ultralevura capsule.

In addition to these epidemiological data, Munoz et al. [17] extensively reviewed the literature to identify previously reported cases of S. cerevisiae or S. boulardii fungemia. The use of the probiotics was reported in nearly one-half of the 60 patients (including the 3 patients they describe), and almost all of the patients had a central venous catheter in place. The overall mortality was 28%.

This review confirms that the most important risk factor for S. cerevisiae fungemia is the use of probiotics. This raises the question of the risk-benefit ratio of these agents in critically ill or immunocompromised patients who are likely to develop an infection after exposure to high amounts of a pathogen with a low virulence. S. boulardii should certainly be contraindicated for patients of fragile health, as well as for patients with a central venous catheter in place. Whether this probiotic still has a place in less severe situations needs to be reassessed.

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References

10. Plein K, Hotz J. Therapeutic effects of Saccharomyces boulardii on mild residual symptoms in a stable phase of Crohn’s disease with...


15. van der Aa KA, Jespersen L. The taxonomic position of *Saccharomyces boulardii* as evaluated by sequence analysis of the D1/D2 domain of 26S rDNA, the ITS1-5.8S rDNA-ITS2 region and the mitochondrial cytochrome-c oxidase II gene. Syst Appl Microbiol 2003;26:564–71.
