

Efficacy and safety of the probiotic *Saccharomyces boulardii* for the prevention and therapy of gastrointestinal disorders

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Abstract: Several clinical trials and experimental studies strongly suggest a place for *Saccharomyces boulardii* as a biotherapeutic agent for the prevention and treatment of several gastrointestinal diseases. *S. boulardii* mediates responses resembling the protective effects of the normal healthy gut flora. The multiple mechanisms of action of *S. boulardii* and its properties may explain its efficacy and beneficial effects in acute and chronic gastrointestinal diseases that have been confirmed by clinical trials. Caution should be taken in patients with risk factors for adverse events. This review discusses the evidence for efficacy and safety of *S. boulardii* as a probiotic for the prevention and therapy of gastrointestinal disorders in humans.

Keywords: efficacy, gastrointestinal disorders, probiotic, *Saccharomyces boulardii*, safety

Introduction

There is increasing evidence that the gastrointestinal microflora is a major regulator of the immune system, not only in the gut, but also in other organs [Gareau *et al.* 2010]. The nonpathogenic yeast *Saccharomyces boulardii* has been prescribed in the past 30 years for prophylaxis and treatment of diarrheal diseases caused by bacteria. Importantly, *S. boulardii* has demonstrated clinical and experimental effectiveness in gastrointestinal diseases with a predominant inflammatory component, indicating that this probiotic might interfere with cellular signaling pathways common in many inflammatory conditions. The goal of this study is to review the clinical evidence for efficacy and safety of *S. boulardii* in the prevention and treatment of gastrointestinal disorders with diverse etiology.

Saccharomyces boulardii as a probiotic

An increasing number of potential health benefits are being attributed to probiotic treatments [Gareau *et al.* 2010; Szajewska *et al.* 2006]. However, only a limited number have been confirmed in well-designed and conducted randomized controlled trials (RCTs) and even less in the pediatric population. *S. boulardii* is a live yeast used extensively as a probiotic and often

marketed as a dietary supplement [McFarland, 2010]. Several mechanisms of action have been identified directed against the host as well as pathogenic microorganisms and include regulation of intestinal microbial homeostasis, interference with the ability of pathogens to colonize and infect the mucosa, modulation of local and systemic immune responses, stabilization of the gastrointestinal barrier function and induction of enzymatic activity favoring absorption and nutrition (Tables 1 and 2) [Czerucka *et al.* 2007; Im and Pothoulakis, 2010; Pothoulakis, 2009].

The multiple prophylactic and therapeutic effects of this probiotic yeast in inflammatory gastrointestinal diseases underline the efficacy of *S. boulardii* in enteric diseases. This efficacy in the prevention and the treatment of acute and chronic gastrointestinal diseases is determined by many factors (Table 3) and has been assessed in several clinical trials (Table 4).

Factors that determine efficacy of *Saccharomyces boulardii* as a probiotic

The efficacy of *S. boulardii* as a probiotic involves many factors, including the intrinsic properties of the yeast (Table 3), its pharmacokinetics (Table 3),

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Table 1. Mechanisms of action of *Saccharomyces boulardii*.

Action of <i>Saccharomyces boulardii</i>	References
Luminal action	
A) Antimicrobial activity	
1) Inhibition of growth of bacteria and parasites	[Chen <i>et al.</i> 2006; Czerucka <i>et al.</i> 1994; Czerucka and Rampal, 2002; Dahan <i>et al.</i> 2003; Dalmaso <i>et al.</i> 2006a; Gedek, 1999a; Rigother <i>et al.</i> 1994; Rodrigues <i>et al.</i> 1996; Mumy <i>et al.</i> 2008; Wu <i>et al.</i> 2008]
2) Reduction of gut translocation of pathogens	[Herek <i>et al.</i> 2004; Geyik <i>et al.</i> 2006]
3) Neutralization of bacterial virulence factors	[Buts <i>et al.</i> 1994; Jahn <i>et al.</i> 1996]
4) Suppression of host cell adherence that interferes with bacterial colonization	[Czerucka <i>et al.</i> 2000; Rodrigues <i>et al.</i> 1996; Wu <i>et al.</i> 2008]
B) Antitoxin effects	
1) Inhibition of toxin receptor binding sites	[Buts <i>et al.</i> 2006; Castagliuolo <i>et al.</i> 1996, 1999; Czerucka <i>et al.</i> 2000; Tasteyre <i>et al.</i> 2002; Wu <i>et al.</i> 2008]
2) Stimulation of antibody production against <i>Clostridium difficile</i> toxin A	[Brandao <i>et al.</i> 1998; Qamar <i>et al.</i> 2001]
3) Direct proteolysis of the pathogenic toxins/Secretion of enzymatic proteins	[Buts <i>et al.</i> 2006; Castagliuolo <i>et al.</i> 1996; Pothoulakis <i>et al.</i> 1993]
a) Produces a serine protease that cleaves <i>C. difficile</i> toxin A	[Pothoulakis <i>et al.</i> 1993]
b) Produces 63 kDa phosphatase that destroys the endotoxin of pathogenic <i>Escherichia coli</i>	[Buts <i>et al.</i> 2006; Castagliuolo <i>et al.</i> 1996]
c) Produces a 120 kDa protein that reduces the effects of cholera toxin	[Czerucka <i>et al.</i> 1994]
C) Cross-talk with normal microbiota	
When <i>S. boulardii</i> is given to antibiotic-exposed mice or patients with diarrhea, normal microbiota is re-established rapidly	[Buts <i>et al.</i> 1986, 1999, 2006; Buts, 2009; Swidsinski <i>et al.</i> 2008]
Trophic action on the intestinal mucosa	
1) Reduces the number of infected cells and stimulates the growth and differentiation of intestinal cells in response to trophic factors	[Barc <i>et al.</i> 2008; Swidsinski <i>et al.</i> 2008]
2) Prevents apoptosis and synthesis of TNF α	[Czerucka <i>et al.</i> 2000; Dahan <i>et al.</i> 2003; Dalmaso <i>et al.</i> 2006b]
3) Reduces mucositis	[Buts <i>et al.</i> 1986, 1999, 2006; Buts, 2009]
4) Restores fluid transport pathways	[Schneider <i>et al.</i> 2005]
5) Stimulates protein and energy production and restores metabolic activities in colonic epithelial cells	[Czerucka <i>et al.</i> 2007; Szajewska <i>et al.</i> 2007; Zanello <i>et al.</i> 2009]
6) Secretes mitogenic factors that enhance cell restitution	[Canonici <i>et al.</i> 2011]
7) Enhances release of brush-border membrane enzymes	[Buts <i>et al.</i> 1998, 2002; Schneider <i>et al.</i> 2005]
8) Stimulates the production of glycoproteins in the brush border	[Buts <i>et al.</i> 1990]
9) Stimulates production of intestinal polyamines	[Buts <i>et al.</i> 1986, 1994, 1999, 2002; Jahn <i>et al.</i> 1996; Schneider <i>et al.</i> 2005]
10) Restores normal levels of colonic short chain fatty acids (SCFAs)	[Buts <i>et al.</i> 1994; Sezer <i>et al.</i> 2009; Breves <i>et al.</i> 2000]
11) Stabilizes gastrointestinal barrier function and strengthens enterocyte tight junctions	[Czerucka <i>et al.</i> 2007; Dahan <i>et al.</i> 2003; Szajewska <i>et al.</i> 2007; Wu <i>et al.</i> 2008; Zanello <i>et al.</i> 2009]
12) Reduces crypt hyperplasia and cell damage in colitis models	[Wu <i>et al.</i> 2008]
13) Decreases intestinal permeability in Crohn's disease patients	[Garcia <i>et al.</i> 2008]

Action of <i>Saccharomyces boulardii</i>	References
Regulation of immune response	
A) By acting as an immune stimulant	
<i>S. boulardii</i> effects on innate immunity	
1) Triggers activation of complement and migration of monocytes and granulocytes	[Caetano <i>et al.</i> 1986]
2) Enhances the number of K�uppfer cells in germfree mice	[Rodrigues <i>et al.</i> 2000]
<i>S. boulardii</i> effects on adaptive immunity	
1) Enhances the mucosal immune response and secretory IgA intestinal levels	[Buts <i>et al.</i> 1990; Czerucka <i>et al.</i> 2007; Generoso <i>et al.</i> 2011; Szajewska <i>et al.</i> 2007; Zanello <i>et al.</i> 2009]
2) Enhances systemic immune response and levels of serum IgG to <i>C. difficile</i> toxins A and B.	[Czerucka <i>et al.</i> 2007; Qamar <i>et al.</i> 2001]
3) Contributes to earlier production of IFN-� and IL-12	[Rodrigues <i>et al.</i> 2000; Thomas <i>et al.</i> 2009]
4) Stimulates regulatory T cells	[Jahn <i>et al.</i> 1996]
5) Inhibits dendritic cell-induced activation of T cells	[Dalmasso <i>et al.</i> 2006a]
6) Modifies migration of lymphocytes in a chronic inflammatory bowel disease model	[Dalmasso <i>et al.</i> 2006a]
7) Modifies lymphocyte adherence to endothelial cells, improves cell rolling and adhesion	[Dalmasso <i>et al.</i> 2006a]
B) By reducing pro-inflammatory responses and promoting mucosal anti-inflammatory signaling effects	
1) Decreases expression of pro-inflammatory cytokines (IL-8, IL-6, IL-1�, TNF-� and IFN-�)	[Dahan <i>et al.</i> 2003; Dalmasso <i>et al.</i> 2006a, 2006b; Mummy <i>et al.</i> 2008; Sougioultzis <i>et al.</i> 2006]
2) Increases expression of the anti-inflammatory cytokine IL-10	[Generoso <i>et al.</i> 2011]
3) Interferes with NF-�B-mediated signal transduction pathways, in immune and colonic epithelial cells	[Buts, 2009; Dahan <i>et al.</i> 2003; Mummy <i>et al.</i> 2008; Pant <i>et al.</i> 2007; Sougioultzis <i>et al.</i> 2006]
4) Blocks activation of ERK1/2 and MAP kinases	[Chen <i>et al.</i> 2006; Kyne <i>et al.</i> 2001; Mummy <i>et al.</i> 2008; Sougioultzis <i>et al.</i> 2006]
5) Decreases NO and inhibits production of inducible NOS	[Girard <i>et al.</i> 2005]
6) Modulates T cell migratory behavior and increases trapping of T helper cells into mesenteric lymph nodes	[Dalmasso <i>et al.</i> 2006a; Fidan <i>et al.</i> 2009; Sougioultzis <i>et al.</i> 2006; Thomas <i>et al.</i> 2009]
7) Stimulates production of anti-inflammatory molecules in human colonocytes such as PPAR-�	[Chen <i>et al.</i> 2006; Lee <i>et al.</i> 2005, 2009; Mummy <i>et al.</i> 2008]
ERK, extracellular signal-regulated kinase; IL, interleukin; INF-�, interferon gamma; IgA, Immunoglobulin A; IGF, insulin growth factor; MAP, mitogen-activated protein; NF-�B, nuclear factor kappa B; NO, nitric oxide; NOS, nitric oxide synthase; PPAR-�, peroxisome proliferator-activated receptor-gamma; TNF�: tumor necrosis factor alpha	

product to product variation, and stability, number of strains used in the probiotic preparation and dose of the probiotic used.

There are many different *Saccharomyces* products commercially available sold as probiotics and *S. boulardii* is usually available in capsules of either lyophilized or heat-dried preparations [McFarland, 2010]. The choice of a high-quality probiotic product is one of the most important factors that determine efficacy of the probiotic. The quality of these products from different sources may vary and many of the commercially available products may lack regulated quality control programs [Marcobal *et al.* 2008; Martins

et al. 2005; Masco *et al.* 2005; Weese, 2003]. Even if the label states it contains *S. boulardii*, a variation in efficacy may occur due to lower than stated dose or inaccurate strain composition [Martins *et al.* 2009]. Selecting high-quality probiotic products can be difficult without access to specific quality control assays for commercially available probiotic products. Selecting products from companies that sponsor original clinical trials may indicate a higher degree of commitment to high-quality products [McFarland, 2010].

The stability of the probiotic product may significantly affect its potency over time. Lyophilized products are stable at room temperature, have the

Table 2. Mechanisms of action of *Saccharomyces boulardii* in specific infections.

Action of <i>Saccharomyces boulardii</i>	References
<i>Clostridium difficile</i> infection	
1) Inhibits toxin A-mediated diarrhea, intestinal inflammation and histological damage by reducing toxin A-receptor binding	[Castagliuolo <i>et al.</i> 1996; Pothoulakis <i>et al.</i> 1993]
2) Releases a protease that cleaves <i>C. difficile</i> toxins and toxin intestinal receptors	[Castagliuolo <i>et al.</i> 1996; Pothoulakis <i>et al.</i> 1993]
3) Stimulates specific intestinal antitoxin A immunoglobulin levels	[Castagliuolo <i>et al.</i> 1996, 1999; Pothoulakis <i>et al.</i> 1993]
4) Inhibits IL-8 production and activation of the MAP kinases Erk1/2 and JNK/SAPK induced by <i>C. difficile</i> toxin A in human colonocytes	[Chen <i>et al.</i> 2006; Qamar <i>et al.</i> 2001]
5) Significantly fewer animals challenged with <i>C. difficile</i> died if given <i>S. boulardii</i> compared with controls	[Castex <i>et al.</i> 1990; Elmer and Corthier, 1991; Rodrigues <i>et al.</i> 1996; Toothaker and Elmer, 1984]
<i>Helicobacter pylori</i> infection	
Alters the structure of <i>H. pylori</i>	[Vandenplas <i>et al.</i> 2009]
<i>Vibrio cholerae</i> infection	
1) Inhibits the effect of <i>V. cholerae</i> toxin and hydroelectrolytic secretions by reducing cAMP activity	[Vidon <i>et al.</i> 1986; Czerucka <i>et al.</i> 1994]
2) <i>S. boulardii</i> and the mammalian CT receptors could be structurally and functionally similar and the yeast binds CT	[Brandao <i>et al.</i> 1998; Czerucka <i>et al.</i> 1994]
Amebic dysentery	
1) Reduces the number of red cells adhering to amoebae	[Rigothier <i>et al.</i> 1994]
2) Decreases the number of amoebae bearing red cells	[Rigothier <i>et al.</i> 1994]
Infection with EHEC	
1) <i>S. boulardii</i> modifies host signaling such as NF- κ B-associated pathways activated by bacterial invasion with EHEC	[Dahan <i>et al.</i> 2002, 2003]
2) Addition to T84 colonocyte monolayers diminishes MLC phosphorylation and decreases transepithelial resistance in response to EHEC	[Dahan <i>et al.</i> 2002, 2003]
Infection with EPEC	
1) Modifies EPEC infection and acts as a receptor decoy for EPEC	[Buts <i>et al.</i> 2006; Canil <i>et al.</i> 1993; Czerucka <i>et al.</i> 2000; Gedek, 1999b]
2) Reduces the number of intracellular EPEC	[Buts <i>et al.</i> 2006; Canil <i>et al.</i> 1993; Czerucka <i>et al.</i> 2000; Gedek, 1999b]
3) Blocks transepithelial resistance and permeability changes, reverses impaired ZO-1 distribution and delays apoptosis of epithelial cells in response to EPEC	[Buts <i>et al.</i> 2006; Canil <i>et al.</i> 1993; Czerucka <i>et al.</i> 2000; Gedek, 1999b]
4) Dephosphorylates LPS from <i>Escherichia coli</i> strain O55B5	[Buts <i>et al.</i> 2006; Canil <i>et al.</i> 1993; Czerucka <i>et al.</i> 2000; Gedek, 1999b]
CT, cholera toxin; EHEC, enterohemorrhagic <i>E. coli</i> ; EPEC, enteropathogenic <i>E. coli</i> ; ERK, extracellular signal-regulated kinase; LPS, lipopolysaccharide; MAP, mitogen-activated protein; MLC, myosin light chain; NF- κ B, nuclear factor kappa B; ZO-1, zonula occludens 1	

Table 3. Properties of *Saccharomyces boulardii* that can determine the efficacy of *S. boulardii*.

Properties of <i>Saccharomyces boulardii</i>	References
1) Survives passage to its target organ (most commonly the colon): although much of the oral dose is destroyed (usually stool levels are 100–1000 times lower than the oral dose), surviving oral doses have been found to be effective (usually at levels over 10 ⁸ organisms/gram stool)	[Gorbach, 2000]
2) Survives at body temperature (37°C): unique advantage of being one of the few yeasts that do best at human body temperatures	[Graff <i>et al.</i> 2008b]
3) In lyophilized form, <i>S. boulardii</i> survives gastric acid and bile	[Graff <i>et al.</i> 2008b]
4) As is the case with all yeasts, <i>S. boulardii</i> is naturally resistant to antibiotics	[Graff <i>et al.</i> 2008b]
5) <i>S. boulardii</i> is resistant to proteolysis	[Buts, 2009]
6) <i>S. boulardii</i> exists in the competitive milieu of the intestinal tract	[Buts, 2009]
7) <i>S. boulardii</i> levels are higher in patients with disturbed intestinal microbiota (due to antibiotic exposure) compared to patients without antibiotic exposure	[Klein <i>et al.</i> 1993]
8) When given orally, achieves steady-state concentrations within three days and is cleared within 3–5 days after it is discontinued	[Blehaut <i>et al.</i> 1989; Elmer <i>et al.</i> 1999b]
9) Some types of fiber (psyllium) increased <i>S. boulardii</i> levels by 22%, while other types of fiber (pectin) showed no effect.	[Elmer <i>et al.</i> 1999a]

Table 4. Clinical efficacy of *Saccharomyces boulardii* in acute and chronic diseases.

Acute diseases
1) Antibiotic-associated diarrhea
2) <i>Clostridium difficile</i> infection
3) Acute diarrhea
4) Persistent diarrhea
5) Enteral nutrition-related diarrhea
6) Traveler's diarrhea
7) <i>Helicobacter pylori</i> infection
Chronic diseases
1) Crohn's disease
2) Ulcerative colitis
3) Irritable bowel syndrome
4) Parasitic infections
a) <i>Amebic colitis</i>
b) <i>Giardiasis</i>
c) <i>Blastocystis hominis</i>
5) Human immunodeficiency virus (HIV)-related diarrhea

advantage of portability and maintain high viability counts over prolonged periods [Graff *et al.* 2008a]. Heat-dried preparations must be refrigerated and may not be stable at room temperature [McFarland, 2010]. A study of *S. boulardii* products found a lyophilized product outperformed three heat-killed *S. boulardii* preparations in terms of pharmacokinetics and higher number of viable cells [Schwenzer, 1998].

All of the RCTs using *S. boulardii* have utilized a single-strain preparation. Although mixtures of probiotics containing *S. boulardii* are available on the market, no RCTs have been performed showing that these mixtures are superior to the single-strain preparations. Preclinical studies in animal models have found promising results in probiotic mixtures containing *S. boulardii* [Bisson *et al.* 2010]. However, possible antagonism between the different probiotics may attenuate the therapeutic responses of the probiotic strains [Kajander *et al.* 2008].

Finally, the dose of *S. boulardii* used can also affect the efficacy of this probiotic [McFarland, 2010]. Different doses of *S. boulardii* used in different studies may explain some of the discrepancies in the efficacy and outcomes between these studies. Unfortunately, the dose of *S. boulardii* used is not reported consistently in all studies while in other studies the dose used is reported heterogeneously between different studies (e.g. number of organisms per 100 ml or number of organisms per day or colony forming units [cfu] per day or grams per day) [McFarland, 2010]. This heterogeneity limits meta-analyses and further analysis of the effect of dose of *S. boulardii* on its efficacy.

Clinical efficacy of *Saccharomyces boulardii* as a probiotic in acute gastrointestinal conditions

S. boulardii has been tested for clinical efficacy in several types of acute gastrointestinal conditions, including antibiotic-associated diarrhea (AAD), *Clostridium difficile* infection (CDI), acute

diarrhea, enteral nutrition-related diarrhea, traveler's diarrhea and *Helicobacter pylori* infection.

Antibiotic-associated diarrhea

AAD is defined as otherwise unexplained diarrhea that occurs in association with the administration of antibiotics [Bartlett, 2002]. Measures to prevent AAD include the use of probiotics. Of the 10 controlled trials in adults using *S. boulardii* for the prevention of AAD, 8 (80%) showed significant efficacy for the prevention of AAD [McFarland, 2010]. The protective effect of *S. boulardii* and the significant relative reduction in AAD compared with controls ranged between 7.4% and 25% [McFarland, 2010]. Other studies failed to demonstrate a significant protective effect of *S. boulardii* and this may be secondary to short or no follow-up after antibiotic exposure [McFarland, 2009]. Two RCTs have assessed the ability of *S. boulardii* to prevent AAD in children and the relative significant increase in prevention of AAD in the *S. boulardii* group compared with controls ranged between 7.6% and 30.1% [Can *et al.* 2006; Kotowska *et al.* 2005].

A recent meta-analysis of the 10 randomized, controlled trials in adults found that *S. boulardii* was significantly protective for AAD with a pooled relative risk (RR) of 0.47 (95% confidence interval [CI] 0.35–0.63, $p < 0.001$) [McFarland, 2010]. Finally, in another meta-analysis from five trials involving 1076 subjects, a significantly protective effect of *S. boulardii* was found (pooled RR = 0.43, 95% CI 0.23–0.78) [Szajewska and Mrukowicz, 2005]. However, although many meta-analyses have concluded that probiotics are effective for preventing AAD [McFarland, 2009], most probiotic meta-analyses have focused on one type of disease indication (e.g. antibiotic associated diarrhea) with a variety of probiotic strains. Thus, we summarized data from meta-analyses that are focused only on the use of *S. boulardii* in preventing AAD and conclude that this probiotic is efficacious for this indication.

Clostridium difficile infection

Probiotics represent a promising approach as an adjunctive therapy for CDI. A meta-analysis of six RCTs of different probiotics, including *S. boulardii* showed that probiotics had a significant efficacy to prevent subsequent recurrences of CDI (RR = 0.59, 95% CI 0.41–0.85, $p = 0.005$) [McFarland, 2006]. However, due to the limited

number of trials, no meta-analysis was conducted for one probiotic strain.

Several pieces of evidence suggest that *S. boulardii* represents the most effective probiotic that can prevent or, together with other agents, treat antibiotic-associated diarrhea and recurrent CDI [McFarland, 2006] through many mechanisms (Table 2).

Animal models of CDI respond to this yeast and case reports or small case series of patients with recurrent CDI treated with *S. boulardii* showed improvement [McFarland, 2010].

The significant relative reduction in recurrent CDI in adults taking *S. boulardii* compared with controls was evaluated in two RCTs and ranged between 19% and 33.3% [McFarland *et al.* 1994; Surawicz *et al.* 2000]. There are only very limited data from one small observational trial in children suggesting that *S. boulardii* may be effective in CDI [Buts *et al.* 1993]. However, according to guidelines no compelling evidence exists to support routine use of probiotics for prevention or treatment of CDI [Cohen *et al.* 2010] especially since some of these studies did not control the dose or duration of either vancomycin or metronidazole for treatment of CDI [McFarland *et al.* 1994] and since scarce data exist on the use of *S. boulardii* for recurrent CDI in humans.

Acute diarrhea

Two RCTs using *S. boulardii* showed that this probiotic may be effective in treating acute adult diarrhea due to a variety of causes and can significantly lower diarrhea severity score compared with controls [Hochter *et al.* 1990; Mansour-Ghanaei *et al.* 2003]. Unfortunately, since the number of trials in this area is small and the etiologies were different in the two trials, only limited conclusions can be reached.

A recent RCT conducted in 100 hospitalized children showed that *S. boulardii* treatment for 5 days significantly reduces the mean duration of acute diarrhea and frequency of stools, and normalizes stool consistency [Htwe *et al.* 2008]. One RCT regarding the efficacy of *S. boulardii* for the prevention of acute diarrhea involved 100 children with acute watery diarrhea and reported a significant difference in the incidence of diarrheal episodes in the group receiving *S. boulardii* compared with the control group during 2 months follow up [Biloo *et al.* 2006].

A meta-analysis based on 5 RCTs (619 participants) [Biloo *et al.* 2006; Kurugol and Koturoglu, 2005; Villarruel *et al.* 2007] indicated that *S. boulardii* significantly reduces the duration of acute childhood diarrhea and the risk of prolonged diarrhea compared with control [Szajewska *et al.* 2007]. A meta-analysis of seven RCTs (944 participants) showed a reduction in the duration of acute childhood diarrhea by approximately 1 day in those treated with *S. boulardii* compared with placebo [Szajewska and Skorka, 2009]. The absence of blinding as well as other factors such as ambulatory care may explain why *S. boulardii* had no effect in a European RCT [Canani *et al.* 2007]. In summary, the findings from RCTs and guidelines from professional pediatric societies indicate that *S. boulardii* may be an effective adjunct therapy in managing acute gastroenteritis in children [Guarino *et al.* 2008].

Persistent diarrhea

Results from two clinical trials indicate that *S. boulardii* improves outcomes in children with persistent diarrhea [Castaneda *et al.* 1995; Gaon *et al.* 2003]. The relative significant reduction in persistent diarrhea in the *S. boulardii* group compared with controls was approximately 50% [Castaneda *et al.* 1995]. These results indicate that *S. boulardii* is useful in the management of persistent diarrhea in children. However, studies with larger populations are needed to determine whether *S. boulardii* therapy alone is also effective in children with persistent diarrhea.

Enteral nutrition-related diarrhea

Diarrhea is a significant problem in patients on total enteral nutrition (TEN) and may involve changes in intestinal short chain fatty acids (SCFAs) [Schneider *et al.* 2005]. Schneider and colleagues reported a significant increase in SCFAs in 10 enteral-fed patients receiving *S. boulardii* compared with 15 healthy controls [Schneider *et al.* 2005]. *S. boulardii*-induced increase of fecal SCFA concentrations may explain the preventive effects of this yeast on TEN-induced diarrhea [Schneider *et al.* 2005]. In three RCTs the relative significant reduction in enteral nutrition-related diarrhea in the *S. boulardii* group compared with controls ranged between 5% and 8.2% [Bleichner *et al.* 1997; Schlotterer *et al.* 1987; Tempe *et al.* 1983]. More studies are needed to elucidate the mechanisms of how *S. boulardii* can prevent TEN-induced diarrhea.

Traveler's diarrhea

A meta-analysis of 12 RCTs of various probiotics (including *S. boulardii*) for the prevention of traveler's diarrhea found a significant reduction in the risk of traveler's diarrhea when probiotics are used (RR = 0.85, 95% CI 0.79–0.91) [McFarland, 2007]. The relative significant reduction in traveler's diarrhea in the *S. boulardii* group compared with controls in two RCTs ranged between 5% and 11% [Kollaritsch *et al.* 1989, 1993]. These limited numbers of studies indicate that probiotics may be more effective in preventing traveler's diarrhea, rather than treating diarrhea once it becomes symptomatic.

Helicobacter pylori infection

A recent meta-analysis involving 14 RCTs (1671 patients) evaluated the role of probiotics in *H. pylori* eradication [Tong *et al.* 2007]. In patients with *H. pylori* infection, probiotic supplementation improved eradication rates and reduced treatment-related side effects and individual symptoms [Tong *et al.* 2007]. In this meta-analysis, only one RCT evaluated *S. boulardii* and found that it decreased the risk of diarrhea when given concomitantly to patients receiving triple eradication therapy for *H. pylori* [Duman *et al.* 2005]. *S. boulardii* induces morphologic changes in *H. pylori* cells consistent with cellular damage [Vandenplas *et al.* 2009] and was shown to cause reduction in *H. pylori* colonization in infected children by 12% [Gotteland *et al.* 2005]. Of four RCTs testing *S. boulardii* in *H. pylori* infections, two were in children [Gotteland *et al.* 2005; Hurdac *et al.* 2009] and two in adults [Cindoruk *et al.* 2007; Cremonini *et al.* 2002]. Although there was no significant difference in *H. pylori* eradication between the *S. boulardii* and placebo groups, a significantly lower relative rate of AAD (16.1–25%) was observed. In a recent meta-analysis, the *H. pylori* eradication rate in the triple therapy group was 71% and increased significantly to 80% with *S. boulardii* supplementation [Szajewska *et al.* 2010]. Thus, *S. boulardii* may not be effective in eradicating *H. pylori* itself, but it is effective in reducing the side effects of the standard triple therapy.

Clinical efficacy of *Saccharomyces boulardii* as a probiotic in chronic diseases

S. boulardii has been tested for clinical efficacy in several types of chronic diseases including Crohn's disease, ulcerative colitis, irritable bowel syndrome (IBS), parasitic infections and human immunodeficiency virus (HIV)-related diarrhea.

Crohn's disease

Recently, the use of probiotics for maintaining remission from active disease in patients with Crohn's disease was given a 'C' recommendation rating level by a panel of experts evaluating the efficacy of the supplements, mostly due to a scarcity of data [Floch *et al.* 2008]. In a small pilot study of 31 patients with Crohn's disease in remission all patients continued their maintenance medications and were randomized to either *S. boulardii* for 3 months or placebo [Garcia *et al.* 2008]. Those treated with *S. boulardii* were found to have a significant reduction in colonic permeability compared with those given placebo, thus reducing the risk of bacterial translocation in these patients [Garcia *et al.* 2008]. Two RCTs tested *S. boulardii* for patients with Crohn's disease [Guslandi *et al.* 2000; Plein and Hotz, 1993]. In a small randomized study of 20 patients with Crohn's disease all patients continued their maintenance medications and were randomized to either *S. boulardii* for 7 weeks or placebo. Patients treated with *S. boulardii* were significantly improved compared with the placebo group [Plein and Hotz, 1993]. Finally, in a study of 32 patients with Crohn's disease who were in remission, significantly fewer patients treated with *S. boulardii* (6%) relapsed than the control group (38%) [Guslandi *et al.* 2000]. Further studies to establish the efficacy of *S. boulardii* in treatment of Crohn's disease are needed.

Ulcerative colitis

Probiotics have been used as an adjunct treatment in an attempt to induce remission in patients with active ulcerative colitis flares [Cain and Karpa, 2011]. In a small pilot study of 25 adults with mild to moderate ulcerative colitis that were treated with a combination of mesalazine and *S. boulardii* for 4 weeks, most (68%) of the patients responded to the probiotic treatment [Guslandi *et al.* 2003]. This pilot study had a promising result, but the implications were uncertain as patients were treated for only a short time, were not followed up for subsequent disease flare ups, and no control group was included. In a small pilot study of 6 patients with ulcerative colitis, a therapeutic regimen including *S. boulardii* and rifaximin for 3 months seemed effective in preventing early flare ups of ulcerative colitis [Guslandi, 2010]. Further controlled studies on a larger number of patients treated for longer periods with this probiotic agent are warranted. Overall, based upon current consensus, the level of evidence for use of probiotics

either to maintain remission or induce remission of ulcerative colitis symptoms is presently limited to a 'C' rating [Floch *et al.* 2008].

Irritable bowel syndrome

Recent evidence suggests a role of the microflora in IBS pathogenesis [Parkes *et al.* 2008]. A meta-analysis of 20 RCTs including 1404 subjects found a pooled RR for improvement in global IBS symptoms in 14 probiotic treatment arms (RR = 0.77, 95% CI 0.62–0.94) [McFarland and Dublin, 2008]. In a double-blind trial of *S. boulardii* versus placebo in the treatment of IBS patients, the probiotic agent significantly improved the quality of life, but did not improve intestinal symptoms [Choi *et al.* 2011]. These findings are inconsistent with those reported in double-blind, RCTs performed earlier in France [Bennani, 1990; Maupas *et al.* 1983]. Along these lines, a recent retrospective analysis suggested that addition of *S. boulardii* to mebeverine can provide superior results in IBS treatment and that the probiotic agent does exert beneficial effects on the quality of life and IBS symptoms [Guslandi, 2011]. More trials using *S. boulardii* for IBS are required to allow solid conclusions for its use in this condition.

Parasitic infections

Little is known about the efficacy of *S. boulardii* against protozoal infections but this probiotic seems to have a beneficial effect in amebiasis, giardiasis and infection with *Blastocystis hominis*. In adults, co-administration of lyophilized *S. boulardii* with conventional treatment in acute amebic colitis significantly decreased the duration of symptoms and cyst carriage after 4 weeks [Mansour-Ghanaei *et al.* 2003]. A prospective RCT in patients with amebic colitis showed that addition of *S. boulardii* to metronidazole enhanced clearance of cysts and decreased the mean duration of diarrhea, fever and abdominal pain [Dinleyici *et al.* 2009].

In a small clinical study of symptomatic children with *Blastocystis hominis* infection *S. boulardii* had potential beneficial effects in symptoms and number of parasites [Dinleyici *et al.* 2011].

The combination therapy of *S. boulardii* in addition to metronidazole in patients with giardiasis resulted in a disappearance of *Giardia* cysts 2 weeks after start of the treatment in contrast to

17.1% of patients treated with 10 days metronidazole as monotherapy who still had *Giardia lamblia* cysts in the stool [Besirbellioglu *et al.* 2006]. In another clinical trial of 40 children who received tinidazole for giardiasis of 3 or 4 weeks duration, the percentage of children with only one to three bowel movements per day was significantly higher in the *S. boulardii* group compared with the placebo group (65% versus 15%) [Castaneda *et al.* 1995]. However, all of the studies regarding use of *S. boulardii* for treatment of parasitic infections are small and the reported results need to be confirmed by larger studies.

HIV-related diarrhea

Patients with HIV-associated diarrhea seem to be one group that requires a higher than typical dose of *S. boulardii*. In a blinded, placebo-controlled study in 11 HIV-positive patients who had chronic diarrhea, lower doses of *S. boulardii* were not as effective compared with 6 patients who reported that diarrhea was controlled while taking 3 g/day *S. boulardii* after 1 month [Elmer *et al.* 1995]. In a RCT of 35 adult patients with acquired immune deficiency syndrome (AIDS) and chronic diarrhea, 61% of patients given *S. boulardii* had their diarrhea resolved compared with patients on placebo (12%) [Saint-Marc *et al.* 1991]. Further confirmation on whether higher doses of *S. boulardii* may benefit patients with HIV-related diarrhea is needed since this observation is based on very limited data.

Safety of *Saccharomyces boulardii* as a probiotic

Although no adverse effects were observed in any of the clinical trials with *S. boulardii*, the administration of *S. boulardii* is not without risk. A recent systematic review documented that probiotic products such as *S. boulardii*, have been shown to increase the risk of complications in specific patient groups such as immunocompromised subjects [Whelan and Myers, 2010]. *Saccharomyces* fungemia is the most severe complication secondary to administration of the probiotic especially in patients with severe general or intestinal disease who had an indwelling catheter [Hennequin *et al.* 2000].

Up to now, almost 100 cases of *S. boulardii*-associated fungemia have been reported [Vandenplas *et al.* 2009]. 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 workers [Hennequin

et al. 2000; Herek *et al.* 2004]. Indeed, the simple act of opening a packet of *S. boulardii* can produce air contamination that may pose environmental risk especially for immunocompromised patients [Hennequin *et al.* 2000]. Once the diagnosis is made, fungemia with *S. boulardii* can effectively be treated with antimycotic medication, although treatment failure with fluconazole has been reported [Burkhardt *et al.* 2005].

A rare gastrointestinal allergic reaction was also recently reported after *S. boulardii* was given to an infant with a prior diagnosis of food protein-induced enterocolitis syndrome [Hwang *et al.* 2009].

Overall, *S. boulardii* is safe for use in otherwise healthy populations and fungemia with *S. boulardii* has not been reported, to the best of the authors' knowledge, in immunocompetent patients. Caution should be taken in patients with risk factors for adverse events (e.g. patients with central venous catheters or increased bacterial translocation) [Venugopalan *et al.* 2010]. Institutional guidelines are needed to address the potential safety issues related to *S. boulardii* use [Venugopalan *et al.* 2010].

Conclusions

Several clinical trials and experimental studies displayed the role of *S. boulardii* as a good biotherapeutic agent allowing to prevent and/or treat several gastrointestinal diseases. *S. boulardii* mediates effects which resemble the protective effects of the normal healthy gut flora. Although the administration of *S. boulardii* can be associated with fungemia, no adverse effects were observed in any of the clinical trials. Caution should be taken in patients with risk factors for adverse events, such as immunocompromised patients. Larger prospective, placebo controlled clinical trials could elucidate the mechanisms of action of the yeast and suggest new therapeutic applications.

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Conflict of interest statement

Dr Kelesidis has no conflicts of interest to declare. Dr Pothoulakis was a paid consultant with Merck and Optimer Pharmaceuticals and a paid speaker for the Postgraduate Institute for Medicine

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