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EDITORIAL

Systematic review and meta-analysis of *Saccharomyces boulardii* in adult patients

Lynne V McFarland

Lynne V McFarland, Department of Health Services Research and Development, Puget Sound Veterans Administration Healthcare System, Seattle, WA 98101, United States; Department of Medicinal Chemistry, Box 357610, School of Pharmacy, University of Washington, Seattle, WA 98195, United States
Author contributions: McFarland LV wrote this paper.
Correspondence to: Lynne V McFarland, PhD, Department of Health Services Research and Development, Puget Sound Veterans Administration Healthcare System, S-152, 1100 Olive Way #1400, Seattle, WA 98101, United States. lynne.mcfarland@va.gov
Telephone: +1-206-2771095 Fax: +1-206-7642935
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Abstract

This article reviews the evidence for efficacy and safety of *Saccharomyces boulardii* (*S. boulardii*) for various disease indications in adults based on the peer-reviewed, randomized clinical trials and pre-clinical studies from the published medical literature (Medline, Clinical Trial websites and meeting abstracts) between 1976 and 2009. For meta-analysis, only randomized, blinded controlled trials unrestricted by language were included. Pre-clinical studies, volunteer studies and uncontrolled studies were excluded from the review of efficacy and meta-analysis, but included in the systematic review. Of 31 randomized, placebo-controlled treatment arms in 27 trials (encompassing 5029 study patients), *S. boulardii* was found to be significantly efficacious and safe in 84% of those treatment arms. A meta-analysis found a significant therapeutic efficacy for *S. boulardii* in the prevention of antibiotic-associated diarrhea (AAD) (RR = 0.47, 95% CI: 0.35-0.63, $P < 0.001$). In adults, *S. boulardii* can be strongly recommended for the prevention of AAD and the traveler's diarrhea. Randomized trials also support the use of this yeast probiotic for prevention of enteral nutrition-related diarrhea and reduction of *Heliobacter pylori* treatment-related symptoms. *S. boulardii* shows promise for the prevention of *C. difficile* disease recurrences; treatment of irritable bowel syndrome, acute adult diarrhea, Crohn's disease, giardiasis, human immunodeficiency virus-related diarrhea; but more supporting evidence is recommended for these indications. The use of *S. boulardii* as a therapeutic probiotic is evidence-based for both efficacy and safety for several types of diarrhea.

Key words: Probiotic; Diarrhea; *Saccharomyces boulardii*; Adult patients; Meta-analysis

Peer reviewer: Andrew S Day, MB, ChB, MD, FRACP, AGAF, Associate Professor, Department of Paediatrics, University of Otago, Christchurch, PO Box 4345, Christchurch 8140, New Zealand

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INTRODUCTION

Probiotics have become increasingly popular in the US and are rapidly reaching levels of use in Europe and Asia, which have a longer history of use compared with the US[1-3]. Probiotics are "live microorganisms, which when administered in adequate amounts, confer a health benefit on the host"[4,5]. In one survey, of 435 users of dietary supplements, 50% of women and 33% of men reported use of probiotics[6].

Probiotics are generally recommended to help strengthen host systems and assist in recovery from certain diseases. However, the general public and many health care providers are still confused about how best to utilize probiotics and which ones are effective for specific diseases. There are several challenges in choosing the appro-

priate probiotic; including the wide diversity of probiotic strains, quality control of commercially-available probiotic products and the degree of evidence-based trials for each disease and probiotic. The ability of an organism to be an effective probiotic has been found to be strain-specific and microbial organisms are defined by their genus, species and strain. For example, *Lactobacillus rhamnosus* (*L. rhamnosus*) GG is a specific bacterial strain, which has been shown to be an effective probiotic for several diarrheal diseases, but other strains within the *L. rhamnosus* species may not be an effective probiotic. Similarly, other species under the same genus (*Lactobacillus*) may not be effective probiotics[7]. To add to this confusion, probiotic products are available in diverse forms: capsules of freeze-dried or lyophilized cultures, heat-dried culture supernatants, mixed in diary food (such as yogurts, cheese, milks, or ice cream) or other food (kefir, chocolate, wafers)[8-10]. The variety of probiotic products are also regulated under different guidelines according to the ways of use (food, dietary supplement, over-the-counter use or prescription). Different standards of quality assurance also vary with the type of product, indication for use and country.

Despite these challenges, the awareness of probiotics as a therapeutic modality has increased dramatically and the frequency of peer-reviewed randomized clinical trials have kept abreast with the global interest in this innovative method of therapy. Numerous probiotic strains have been investigated for clinical efficacy, including multiple bacterial strains: *Lactobacilli*, *Bifidobacteria*, *Streptococci*, Clostridia and fungal strains: *Saccharomyces boulardii (S. boulardii), S. cerevisiae*, and *Monascus purpureus*[11-13]. This review examines evidences for Saccharomyces probiotics and focuses on *S. boulardii* for the efficacy and safety of different diseases in adult patients. The two goals of this study were: (1) to provide guidance for clinicians and patients on how to appropriately use *S. boulardii* as a therapeutic probiotic and (2) to review the evidence for efficacy and safety of *S. boulardii* for various disease indications in adults.

SEARCH STRATEGY FOR SYSTEMATIC REVIEW

PubMed, Medline and Google Scholar were searched for articles unrestricted by language from 1976 to 2009. Three on-line clinical trial registers were searched: Cochrane Central Register of Controlled Trials (www.cochrane.org), metaRegister of Controlled Trials (www.controlled-trials.com/mrct) and National Institutes of Health (www.clinicaltrials.gov). Secondary and hand searches of reference lists, other studies cross-indexed by authors, reviews, commentaries, books and meeting abstracts also were performed. Search terms included: *Saccharomyces boulardii*, probiotics, yeast, diarrhea, risk factors, randomized controlled trials, placebo-controlled, and associated author names. Search strategies were broad-based initially, then narrowed to the disease of interest to increase the search network[14].

META-ANALYSIS

If sufficient numbers of clinical trials (> 5) were found on one type of disease indication, a meta-analysis for the efficacy of *S. boulardii* was performed; otherwise a systematic review was done. The procedure for the meta-analysis followed standard meta-analysis methodology with clearly delineated parameters, *a priori* inclusion and exclusion criteria and standardized data extraction[15,16]. Abstracts of all citations and retrieved studies were reviewed and rated for inclusion. In some cases, only published abstracts from meetings were available. Published abstracts from meetings were included to lessen the potential for publication bias due to failure to publish negative findings. Information on study design, methods, interventions, outcomes, adverse effects and treatments was extracted from each article using a standardized extraction table. When necessary, authors were contacted for data not reported in the original article.

The primary objective of the meta-analysis was to determine the overall efficacy of *S. boulardii* within one specific type of disease indications (antibiotic-associated diarrhea, *Clostridium difficile* disease, traveller's diarrhea, irritable bowel syndrome, inflammatory bowel disease or other types of diarrhea). Inclusion criteria were: randomized, controlled, blinded efficacy trials in humans published as full articles or meeting abstracts in peer-reviewed journals. Exclusion criteria included: use of other strains of Saccharomyces (such as *Saccharomyces cerevisiae*) or other strains of probiotics, pre-clinical studies, safety studies, case reports or case series, phase I studies in volunteers, reviews, duplicate reports, trials of unspecified treatments, uncontrolled studies, prebiotic treatments only (no living organisms) or insufficient data in article.

To estimate pooled relative risks across studies, heterogeneity between and within trials was evaluated using the Cochrane Q and I^2 tests[17]. Relative risks (RR) and 95% confidence intervals (CI) were calculated using the Mantel-Haenszel method. The relative risks of responding to *S. boulardii* therapy were pooled using a random-effect model if significant heterogeneity was found or a fixed-effect model if the studies were homogenous. P values less than 0.05 were considered significant. Analyses were performed using Stata software version 9.2 (Stata Corporation, College Station, Texas). A funnel scatterplot and Begg's test were used to assess publication bias[18].

HISTORY

Saccharomyces cerevisiae strains have a long history of use in baking and brewing preparation, but have only infrequently been investigated for probiotic properties[19,20]. Another closely related strain, *S. boulardii*, was discovered by a French microbiologist, Henri Boulard in 1920 when he was in IndoChina searching for new strains of yeast that could be used in fermenting processes. He was a visitor during a cholera outbreak and noticed that some people who did not develop cholera were drinking a special tea. This tea was

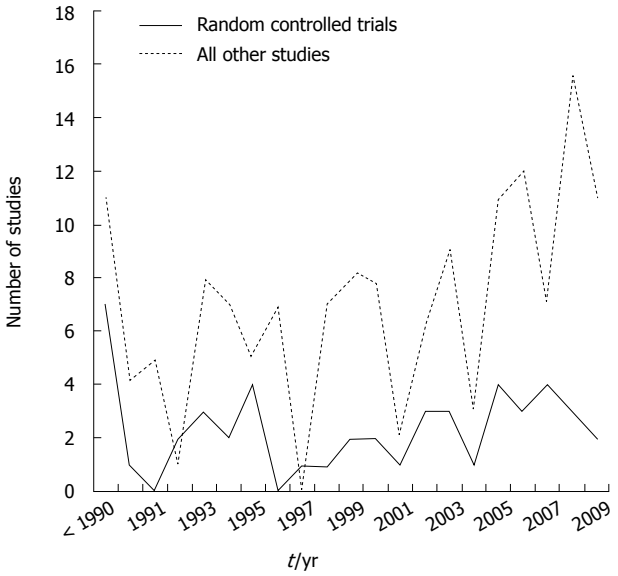

Figure 1 Frequency of peer-reviewed publications on *Saccharomyces boulardii* from 1976 to 2009.

made by taking the outer skin from a tropical fruit (lychee and mangosteens) and cooking them down to make tea. He succeeded in isolating the agent responsible. It was a special strain of yeast he named "*Saccharomyces boulardii*". The patent for this yeast was bought by Laboratories Biocodex in 1947, which began researching and manufacturing protocols. As shown in Figure 1, interest in this strain has increased, as reflected by the increasing number of scientific publications, encompassing both pre-clinical papers in mechanisms of action, animal models of efficacy, pharmacokinetics, early studies in safety and dose-ranging. In addition, there are currently 53 randomized controlled clinical trials, encompassing 8475 subjects, investigating the safety and efficacy of *S. boulardii* in pediatric and adult patients spanning several disease indications, of which 43 (81%) found significant efficacy for *S. boulardii*. As a recent review article on the efficacy of *S. boulardii* was published for pediatric indications[21], this study will focus on *S. boulardii* use in adult patients. There have been 27 randomized controlled trials, with 31 treatment arms testing *S. boulardii* in adult patients for a variety of diseases and most (84%) found a significantly protective efficacy of this probiotic. There have been only a few randomized clinical trials using other strains of Saccharomyces probiotics, which will be discussed later in this paper.

TAXONOMY

Probiotics may be either bacterial or yeast microbes. Yeast probiotics, such as *S. boulardii*, are different from bacterial probiotics (different physiologic structures, large in size, do not acquire antibiotic-resistant genes and are not affected by antibiotics)[12]. Not only is there a confusing array of probiotic products on the global market, but the taxonomy of Saccharomyces strains has been debated[22]. One strain has received considerable discussion about its valid nomenclature[23,24]. It was originally named *S. boulardii* in the 1950's. Advances in typing methods opened a debate as to whether this strain should be reclassified as a strain of *S. cerevisiae* or remain a separate species. Early work using PCR electrophoretic karotyping or rRNA sequencing methods reported that *S. boulardii* was indistinguishable from other strains of *S. cerevisiae*[24,25]. Newer metabolomic tools (microsatellite polymorphism analysis and retrotransposon hybridization analyses) show that *S. boulardii* has a unique clustering different from other strains of *S. cerevisiae*[26-28]. In addition, *S. boulardii* differs from other strains of *S. cerevisiae* by several metabolic and genetic characteristics[29,30]. *S. boulardii* persists longer in gnotobiotic mice models (10 d) compared with rapid clearance of other strains of *S. cerevisiae* (< 1 d)[31]. *S. boulardii* is also different physiologically and metabolically and its optimum growth temperature is 37℃ and it is resistant to low pH and is tolerant to bile acids; whereas other strains of *S. cerevisiae* prefer cooler temperatures (30-33℃) and do not survive well in acid pH ranges[32-34]. *S. boulardii* can be distinguished from other strains of *S. cerevisiae* by advanced typing methods, by differences in metabolism and physiology and by the ability to have anti-pathogen effects (as discussed in the mechanisms of action section).

GUIDELINES FOR CHOOSING APPROPRIATE PROBIOTICS

Challenges in providing guidance to patients regarding the appropriate choice of probiotic include the wide diversity of available products on the market, variances in quality control, stability and formulations in those products, and the requirement to match the type of probiotic with the disease indication. The efficacy of probiotics have been shown to be both strain-specific and disease-specific[11,35,36].

Product to product variation

There are many different Saccharomyces products available commercially. Table 1 lists some examples of products that contain *S. boulardii*, sold as probiotics either as lyophilized or heat-dried powders in capsules, or as one of several strains in a probiotic mixture in capsules or in liquid beverages[12,13,21,37-66]. The quality of these products from different sources have been found to vary. Choosing a probiotic product from a manufacturer with a regulated quality control program is a sound policy. Unfortunately, many of the products available commercially may lack regulated quality control programs. Studies of other probiotics have found a wide diversity in both quality and contamination in products available on the Internet[67]. Marcobal *et al*[68] tested 14 commercial probiotics in the US and found 93% were incorrectly labeled (57% had contaminants and 36% did not list strains on the label). Masco *et al*[69] tested 58 different probiotic products from Europe, UK, Asia, Japan and Canada and found only 38% had the dose stated on the label and 29% did not contain strains listed on the label. Not all products were found to have high standards of manufacture and quality control, as only some conform to Good Manufacturing Practices.

Table 1 Examples of commercially available probiotics containing "*Saccharomyces boulardii*"

Product name	Probiotic strain	Manufacturer	Stable at room temp[1]	Facility certified	Strain confirmed	Colony forming unit (cfu) per mg capsule or mL	Original strain-specific studies	Degree of clinical evidence[2]
Single strain								
Florastor® (US) Perenterol® (Germany) Reflor® (Turkey) Ultra-Levure® (Asia)[3]	*S. boulardii* lyo	Biocodex (France)	Yes	EU GMP	Microsatellite sequency polymorphism [28,29]	5×10^9/ 250 mg	Multiple [37-62]	A
SB+MOS	*S. boulardii*	Jarrow Formulas (Los Angeles, CA) and Gnosis (Italy)	No	EU GMP	Not stated	1.5×10^9	One study[63]	C
Saccharomyces boulardii	*S. boulardii*	Kirkman (Oregon)	No	GMP	DNA fingerprint	3×10^9/ 150 mg	None	F
Saccharomyces boulardii	*S. boulardii*	Allergy Research Group (CA)/NutriCology (CA)	No	GMP	DNA fingerprint	3×10^9/ 150 mg	None	F
Saccharomyces boulardii	*S. boulardii*	Klaire Labs (Reno Nevada)	No	GMP ISO 9001	Ribotyping	3×10^9/ 150 mg	None	F
In mixtures of probiotics								
Protecflor® (Canada) Erce Flora® (Belgium)	*S. cerevisiae boulardii* CNCM I-1077) + *L. rhamnosus* + *L. acidophilus* + Bifido. strain	Institut Rosell-Lallemand (Quebec, Canada)	Not stated	Canadian GMP	Not stated	10^9/2 mL	Two studies [64,65]	D
MitoMix®	*S. boulardii* and *Pediococcus acidilactici*	Imagilin Technology (Maryland)	Yes	Not stated	Not stated	2.3×10^9/ capsule	One study[66]	D
Primal Defense™	*S. boulardii* with 13 other strains[4]	Garden of Life (FL)	Yes	Not stated	No (only certified "organic")	Total 1×10^9 per 410 mg	None	F
Pro-Bio Defense™	*S. boulardii* + 7 other strains[5]	Kirkman (OR)	No	GMP	DNA fingerprint	Total: 2×10^{10}/cap, no data on SB cfu	None	F
ABX Support™	*S. boulardii* + *L. rhamnosus* + *Bifido. bifidum* + *Bifido. breve*	Klaire Labs (NEV)	No	GMP ISO 9001	Ribotyping	5×10^9/ 300 mg	None	F
Kombucha fermented tea	*S. boulardii* + *L. bacterium* + blue-green algae	Millennium Products, Inc.	No	No	Not stated	1×10^9 per 16 oz.	None	F

[1]Products not stable at room temperature require refrigeration, probably heat-dried. Products stable at room temperature are typically packaged in blister packs and are lyophilized; [2]Degree of evidence: A = at least two randomized, controlled clinical trials in patients; B = one randomized controlled clinical trial in patients, C = case reports, uncontrolled randomized trials or open safety/kinetic studies in patients or volunteers, D = *in vivo* animal model or *in vitro* studies only, E = expert opinion only, F = no direct evidence; [3]A few examples, Biocodex has over 40 brand names worldwide; [4]Other strains in Primal Defense include: 11 strains of *Lactobacilli* (*L. acidophilus, L. bulgaricus, L. lactis, L. plantarum, L. casei, L. lactis, L. leichmannii, L. brevis, L. caucasicus, L. fermenti*, *L. helveticus* and 1 strain each: *Bifidobacterium bifidum, Bacillus subtilis, Bacillus lichenformis*); [5]Other strains in Pro-Bio Defense include: 5 strains of *Lactobacilli* (*L. plantarum, L. rhamnosus, L. acidophilus, L. casei, L. bulgaricus*) and *Bifidobacterium lactis* and *Streptococcus thermophilus*. GMP: Good manufacturing practices.

Although most products state they contain at least 1×10^9 *S. boulardii*/mg, independent assays have determined 50% of the products contained a dose less than on the label. In one study comparing six *S. boulardii* products, all had identical PCR typing profiles, but only 50% [Floratil (Merck), Flomicin (NeoChemical), and Florazin (Herald's)], had the same concentration identified on their label. One product [Lactipan (Sigma Pharm)] had 2×10^4 fewer *S. boulardii* than stated on its label. One product [Floratil (Merck)], had the highest concentration (1×10^9/100 mL) and maintained high levels (9.5×10^8) six months later[70]. 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. Four *S. boulardii* products were tested (along with one *S. cerevisiae* product) in Brazil. Only two (50%) of the *S. boulardii* products were protective in a *Salmonella typhimurum* mouse model (two *S. boulardii* products were ineffective, as well as the one *S. cerevisiae* product)[71]. Without access to specific quality control assays for commercially available probiotic products, the choice of a high quality product can be difficult. One method of selecting a probiotic product is to find a product in which the manufacturing company has sponsored original clinical trials, as this indicates a degree of commitment that may not be present in companies that do not sponsor original research. As shown in Table 1, only a few *S. boulardii* probiotic products are supported by original research. Although at present, most probiotic clinical trials are sponsored by private companies, as more national funding becomes available, this situation may change.

Stability

How the probiotic product is manufactured may significantly affect its potency over time (shelf-life). Probiotics may be available as lyophilized preparations, heat-dried preparations or contained in diary or drink food products.

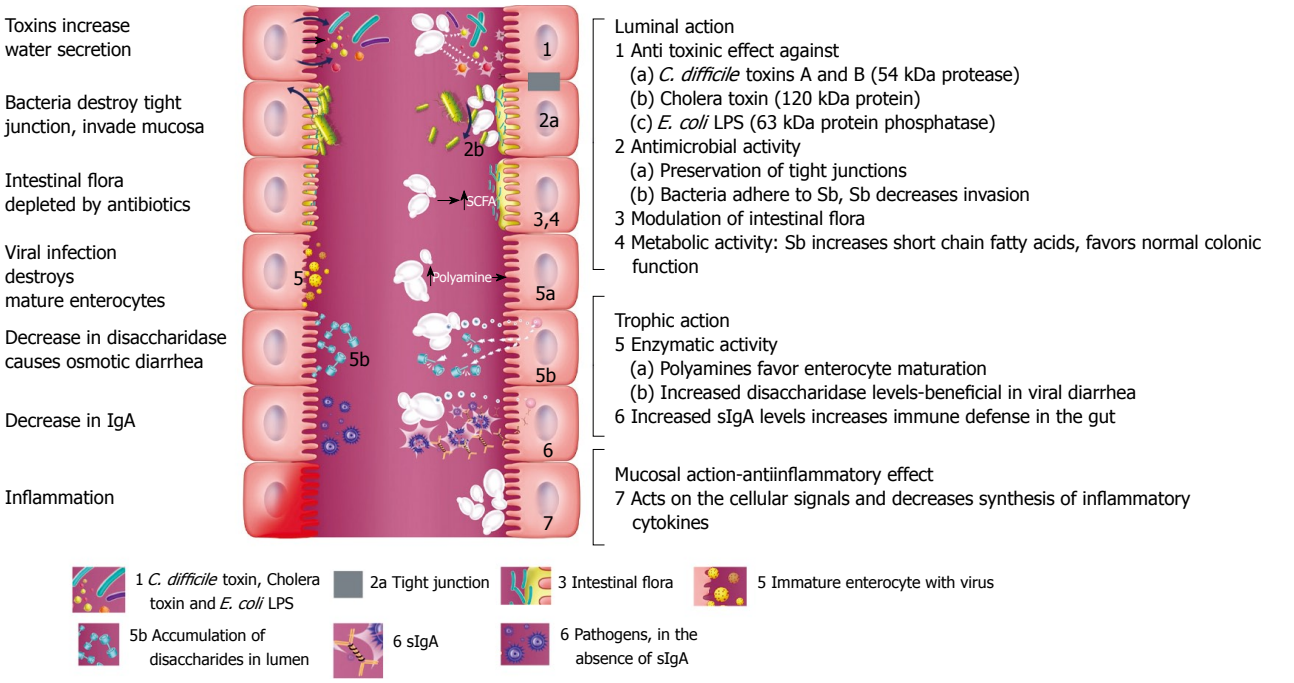

Figure 2 Schematic of intestinal tract, illustrating the different potential mechanisms of action of *Saccharomyces boulardii* (Sb). On the left, effects of different pathogenic microbes are depicted. On the right, seven different protective effects of *S. boulardii* are depicted. Within the lumin of the intestine, *S. boulardii* may degrade toxins of pathogens, interfere with pathogenic adherence, modulate normal microbiota and preserve normal intestinal physiology. *S. boulardii* may also indirectly restore normal short chain fatty acid (SCFA) balance. *S. boulardii* may also increase secretory IgA (sIgA) levels or act as an immune regulator by influencing cytokine levels.

S. boulardii is usually available in capsules of either lyophilized or heat-dried preparations. Heat-dried capsule products may be identified by their labels, which usually state that the products should be refrigerated after opening and they lose their potency rapidly. Lyophilized preparations of *S. boulardii* are stable over one year at room temperature, as long as it is protected from moisture[72]. Lyophilized products are stable at room temperature and have the advantage of portability and convenience and maintain high viability counts over prolonged periods. Heat-dried preparations are not stable at room temperature and must be refrigerated. A study of four *S. boulardii* products in Germany found a lyophilized product [Perenterol Forte (Thiemann)] outperformed three heat-killed *S. boulardii* preparations in terms of higher viable cells and quicker start-up times[73].

Single strain or probiotic "cocktails"

As shown in this review, all the randomized controlled trials using *S. boulardii* probiotics have utilized a single strain preparation. Although mixtures of probiotics, which may contain *S. boulardii*, are available on the market, no randomized controlled trials have been done showing that these mixtures are superior to the single stain preparations. Pre-clinical studies in animal models have found promising results in a probiotic mixture (*L. rhamnosus*, *L. acidophilus, Bifidobacterium* and *S. boulardii*) for reducing *E. coli* diarrhea in rats, but no human clinical trials have been performed with this mixture[65]. Another potential limitation to probiotic mixtures is antagonism between the different probiotic strains and conflicting mechanisms of actions that may tend to attenuate the therapeutic responses of the probiotic strains[74].

Mechanisms of action

An advantage of probiotics is that they are living organisms incorporating a delivery system (most probiotics survive to the target organ) bringing an arsenal of anti-pathogenic strategies into play. *S. boulardii* has several different types of mechanisms of action (Figure 2) which may be classified into three main areas: luminal action, trophic action and mucosal-anti-inflammatory signaling effects[8,75-77]. Within the intestinal lumen, *S. boulardii* may interfere with pathogenic toxins, preserve cellular physiology, interfere with pathogen attachment, interact with normal microbiota or assist in reestablishing short chain fatty acid levels. *S. boulardii* also may act as an immune regulator, both within the lumen and systemically.

Anti-toxin effects: *S. boulardii* may interfere with pathogenesis within the intestinal lumen by several mechanisms: either by blocking pathogen toxin receptor sites[78], or acting as a decoy receptor for the pathogenic toxin[79] or by direct destruction of the pathogenic toxin. Castagliuolo *et al*[80] found a 54 kDa serine protease produced by *S. boulardii* directly degrades *C. difficile* toxin A and B. The efficacy of other strains of Saccharomyces has also been investigated. Only *S. boulardii* produces a protease capable of degrading *Clostridium difficile* toxins and receptors sites on the enterocyte cell surface, unlike other strains of Saccharomyces[78,81]. Buts *et al*[82] found a 63 kDa phosphatase produced by *S. boulardii* destroys the endotoxin of pathogenic *E. coli*. Several investigators showed that *S. boulardii* could reduce the effects of cholera toxin and this may be due to a 120 kDa protein produced by *S. boulardii*[83,84].

Antimicrobial activity: *S. boulardii* is capable of directly or indirectly interfering with intestinal pathogens. *S. boulardii* may directly inhibit the growth of pathogens (such as *Candida albicans*, *Salmonella typhimurum*, *Yersinia enterocolitium*, *Aeromonas hemolysin*[43,85,86]). In animal models testing for the ability to inhibit pathogen growth, several studies using non-*S. boulardii* strains of *S. cerevisiae* did not find any effect unlike the protective effects of *S. boulardii*[31,70]. A few studies have tested other strains of *S. cerevisiae* and found promising results. Brandao *et al*[79] tested *S. cerevisiae* strain W303 in rats and found less histologic damage due to cholera toxin compared with saline controls, but no clinical trials have been done using this strain. *S. boulardii* may also act by enhancing the integrity of the tight junction between enterocytes, thus preserving intestinal integrity and function[87,88]. Wu *et al*[88] found less crypt hyperplasia and cell damage in a *Citrobacter rodentium*-induced mice model of colitis when mice were treated with 1×10^9 *S. boulardii* per day for 7 d. Garcia Vilela *et al*[62] found decreased intestinal permeability when patients with Crohn's disease were given *S. boulardii* (1.6×10^9/d for 4 mo) compared with placebo. *S. boulardii* has also been shown to reduce the translocation of pathogens in rat and pig animal models[64,89,90]. *S. boulardii* can also interfere with pathogenic attachment to intestinal receptor sites[88,91,92]. Gedek *et al*[93] also found that *S. boulardii* acts as a decoy by causing EPEC cells to directly bind to the surface of *S. boulardii* cells rather than enterocytes.

Cross-talk with normal microbiota: Newer techniques, including metagenomics and PCR probes have documented that a typical human may carry over 40 000 bacterial species in the collective intestinal microbiome[94]. The normal intestinal flora has many functions, including digestion of food, but the one that is most germane for this discussion is called "colonization resistance"[77,95,96]. This involves the interaction of many bacterial microflora and results in a barrier effect against colonization of pathogenic organisms. Normal microflora may act by competitive exclusion of nutrients or attachment sites, produce bacteriocins, or produce enzymes detrimental to pathogenic growth. Factors that disrupt this protective barrier, for example antibiotic use or surgery, results in host susceptibility to pathogen colonization until such time as the normal microflora can become re-established. Typically, it takes six to eight weeks for normal microbiota to recover after antibiotic exposure or disease resolution[97]. Probiotics are uniquely qualified to fit into this window of susceptibility and may act as surrogate normal microflora until recovery is achieved. *S. boulardii* has no effect on normal microbiota in healthy human controls[98,99]. In contrast, when *S. boulardii* is given to antibiotic-shocked mice or patients with diarrhea, normal microbiota is re-established rapidly[99,100].

Restoration of metabolic activities: *S. boulardii* has been shown to be able to increase short chain fatty acids (SCFA), which are depressed during disease, indicating altered colonic fermentation[98,101,102].

Trophic effects: *S. boulardii* can reduce mucositis[103], restore fluid transport pathways[84,101,104], stimulate protein and energy production[105], or act through a trophic effect by releasing spermine and spermidine or other brush border enzymes that aid in the maturation of enterocytes[106,107].

Immune response: *S. boulardii* may also regulate immune responses, either acting as an immune stimulant or by reducing pro-inflammatory responses. *S. boulardii* may cause an increase in secretory IgA levels in the intestine[56,108-110]. It has also been found associated with higher levels of serum IgG to *C. difficile* toxins A and B[111]. *S. boulardii* may also interfere with NF-κB-mediated signal transduction pathways, which stimulate pro-inflammatory cytokine production[76,112,113]. Chen *et al*[114] found that *S. boulardii* blocks activation of ERK1/2 and MAP kinases, which typically stimulate IL-8 production and cell necrosis in mice ileal loop models and in *in vitro* models. *S. boulardii* has also been shown to cause the trapping of T helper cells into mesenteric lymph nodes, thereby reducing inflammation[115].

Properties of *S. boulardii*

To be an effective probiotic, it must survive passage to its target organ (most commonly the colon). Organisms need to survive at body temperature (37℃), be resistant to stomach acids and bile acids, and exist in the competitive milieu of the intestinal tract. Probiotic strains of Saccharomyces have been shown to have these abilities. Although the optimal temperature for most strains of Saccharomyces range from 22-30℃, *S. boulardii* survives best at 37℃, giving it a unique advantage of being one of the few yeasts that do best at human body temperatures.

Survival to target sites: 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/g stool)[116]. *S. boulardii* is resistant to antibacterial agents and survives gastric acidity[34,117]. In human volunteers, the concentration in the colon was found to be dose-dependent[118]. When *S. boulardii* was given to healthy volunteers at doses typically used therapeutically ($1\text{-}2 \times 10^{10}$/d), colonic levels were 2×10^8/g stool[118]. Few clinical trials using probiotics have documented the level of organisms present in the terminal site (colonic lumen in their study subjects). However, in one trial of patients with recurrent *C. difficile* infection (CDI) given *S. boulardii* (2×10^{10}/d) for 28 d, patients who had a subsequent CDI recurrence were found to have significantly lower numbers of *S. boulardii* (2×10^4/g stool) compared with those without recurrence (1×10^6/g stool)[119].

Pharmocokinetics: *S. boulardii*, when given orally, achieves steady-state concentrations within three days and is cleared within 3-5 d after it is discontinued[34,119,120]. Blehaut *et al*[120] gave eight healthy human volunteers *S. boulardii* (oral dose

of 5×10^9) for six days and followed them for time-to-clearance. They determined *S. boulardii* has half-life of 6 h, fecal steady-state concentrations (2×10^7/g) were reached by day 3 and the yeast was cleared after four days after administration. Klein *et al*[118] confirmed these findings in their studies of human volunteers and also found *S. boulardii* levels were 23 times higher in volunteers with disturbed intestinal microbiota (due to ampicillin exposure) than volunteers who were not given ampicillin. Elmer *et al*[121] found that some types of fiber (psyllium) increased *S. boulardii* levels by 22%, while other types of fiber (pectin) showed no effect.

CLINICAL EFFICACY: ACUTE DISEASES

S. boulardii probiotics have been tested for clinical efficacy in several types of acute diseases including antibiotic-associated diarrhea, *C. difficile* infections, *Helicobacter pylori* (*H. pylori*) disease, acute adult diarrhea, enteral nutrition-related diarrhea, and traveler's diarrhea.

Antibiotic-associated diarrhea

Epidemiology of antibiotic-associated diarrhea: The reported incidence of antibiotic-associated diarrhea (AAD) ranges from 12/100 000 to 34/100[122] depending upon the type of antibiotic, host factors (age, health status, *etc.*), etiology, hospitalization status and presence of a nosocomial outbreak. The highest frequency of AAD is found (26%-60%) during healthcare associated outbreaks, when susceptible patients are clustered by time, exposure and proximity[123]. Healthcare associated (hospital, long-term care facilities, nursing homes) outbreaks of AAD are to be expected because inciting agents (antibiotics), infectious agents and a susceptible patient population are intermixed. Historically, most cases of AAD were reported in hospitalized patients[122]. More recently, although AAD still occurs in hospital settings, rates of 6-33/100 have been reported in outpatient populations[124,125] and lower rates (12/100 000 to 14/100) in non-hospitalized adults[126,127]. Lower rates observed in outpatients may be due to their generally higher health status compared with hospitalized patients and also to the lack of exposure to nosocomial pathogens that commonly contaminate hospital environments. Higher incidences are still found in healthcare associated pediatric and adult patients (ranging from 5-34/100 patients)[128-130].

The clinical presentation of AAD may be mild (uncomplicated diarrhea) or more severe (colitis), or result in toxic megacolon or death[122]. The onset of AAD may occur while the patient is on antibiotics, but delayed-onset AAD is more common[122]. In addition, the onset of AAD may vary according to the type of antibiotic. Elmer *et al*[131] found a variable time of onset using the hamster model of AAD and different types of antibiotics. Early onset of AAD was associated with clindamycin, amoxicillin and ampicillin, while delayed-onset AAD was associated with erythromycin, ciprofloxacin and clarithromycin. Consequences of AAD may result in extended hospital stays, increased medical care costs and increased diagnostic procedures[122,132]. Prevention of AAD has rested on discontinuing the inciting antibiotic or switching to an antibiotic with a narrower spectrum of action, but there are no other current effective preventive measures for AAD.

Efficacy evidence for AAD: There have been ten randomized controlled trials in adults using *S. boulardii* for the prevention of AAD (Table 2)[37,42,44,54,55,58,133-136]. These studies have used a variety of daily doses, durations of treatment, length of follow-up and types of patient population. Of the ten controlled trials, 8 (80%) showed significant efficacy for the prevention of AAD compared with controls. One of the earliest trials by Adam *et al*[37], randomized 388 hospitalized patients to 200 mg of *S. boulardii* [4×10^9 cfu (colony forming units)/d] or placebo for seven days and found a significant reduction in AAD in the *S. boulardii group* (4.5%) compared with the controls (17.5%, $P < 0.05$). The protective effect of *S. boulardii* was confirmed in later studies. Monteiro *et al*[55] enrolled 240 patients receiving oral antibiotics and found significantly fewer patients randomized to *S. boulardii* developed AAD (15.7%) compared with placebo (27.7%, $P < 0.05$). McFarland *et al*[54] enrolled 193 hospitalized patients receiving beta-lactam antibiotics and randomized them to either 1 g of *S. boulardii* or placebo for the duration of the antibiotic treatment plus three additional days. Significantly fewer patients developed AAD while on the beta-lactam antibiotics or in the seven week follow-up period when given *S. boulardii* (7.2%, $P < 0.05$) compared with 14.6% of those given placebo. This study confirmed an earlier study by Surawicz *et al*[58] of 180 hospitalized adults randomized to either *S. boulardii* or placebo for the duration of their antibiotic treatment plus an additional two weeks. Of the 23% patients who were contacted 2-3 wk after the study, only one patient given placebo developed delayed-onset AAD. Only 9.5% of those randomized to *S. boulardii* developed AAD compared with 21.8% of those on placebo ($P < 0.05$). Can *et al*[135] enrolled 151 adult inpatients receiving various types of antibiotics, who were then randomized to *S. boulardii* or placebo for the duration of the antibiotic treatment. Significantly fewer patients (1.4%, $P < 0.05$) of those given *S. boulardii* developed AAD compared with the control group (9.0%). Three trials have been in conducted in patients with *H. pylori* infections receiving triple therapy (usually two antibiotics and an acid suppressor), which is associated with a high rate of AAD development. Duman *et al*[44] enrolled 389 patients with peptic ulcer or non-ulcer dyspepsia in nine hospitals in Turkey to observe if lower rates of side-effects could be achieved. This study compared 204 patients who received 1 g of *S. boulardii* (2×10^{10}/d for 2 wk) and triple therapy with 185 controls, who received only the triple therapy. Of the 389 patients, 376 completed the treatment phase and the four-week follow-up. Significantly fewer patients given *S. boulardii* (6.9%) developed AAD compared with the control group (15.6%, $P = 0.007$). Two other randomized controlled trials in adult patients receiving triple therapy for *H. pylori* infections were conducted and both showed a significant reduction in AAD for those treated with *S. boulardii*. Cremonini *et al*[134] randomized 85 *H. pylori* carriers to placebo, *L. rhamnosus* GG, *S. boulardii* or a mix of

Table 2 Randomized, controlled trials for the prevention of antibiotic associated diarrhea (AAD) using *S. boulardii*

Ref.	Treatment groups	Population	Daily dose: cfu/d (mg/d)	Duration (d)	Follow-up (wk)	AAD in *S. boularii* (%)	AAD in controls (%)
Adam *et al*[37]	*S. boulardii* *vs* placebo	388 hospitalized adults, multisite	4×10^9 (200 mg)	7	0	9/199 (4.5)[a]	33/189 (17.5)
Monteiro *et al*[55]	*S. boulardii* *vs* placebo	240 adults, Portugal	(nr) 4 caps/d	6	0	19/121 (15.7)[a]	33/119 (27.7)
Surawicz *et al*[58]	*S. boulardii* *vs* placebo	180 hospitalized adults at one hospital, Washington	2×10^{10} (1000 mg)	abx + 14 d	2-3	11/116 (9.5)[a]	14/64 (21.8)
McFarland *et al*[54]	*S. boulardii* *vs* placebo	193 hospitalized adults (1 or more beta-lactam antibiotics), 4 hospitals	2×10^{10} (1000 mg)	abx + 3 d	7	7/97 (7.2)[a]	14/96 (14.6)
Lewis *et al*[133]	*S. boulardii* *vs* placebo	72 enrolled, 69 done; elderly patients	4.5×10^9 (226 mg)	14	0	7/33 (21)	5/36 (13.9)
Cremonini *et al*[134]	*S. boulardii* *vs* placebo	43 *H. pylori* + adults on triple therapy	5×10^9 (nr)	14	2	1/22 (5)[a]	6/21 (30)
Duman *et al*[44]	*S. boulardii* *vs* placebo	389 adults in Turkey with *H. pylori* + peptic ulcers, all received triple therapy	2×10^{10} (1000 mg)	14	4	14/204 (6.9)[a]	28/180 (15.6)
Can *et al*[135]	*S. boulardii* *vs* placebo	151 adult inpatients	1×10^{10} (500 mg)	abx	4	1/73 (1.4)[a]	7/78 (9.0)
Cindoruk *et al*[42]	*S. boulardii* *vs* placebo	124 adults with *H. pylori* + dyspepsia	2×10^{10} (1000 mg)	14	6	9/62 (14.5)[a]	19/62 (30.6)
Bravo *et al*[136]	*S. boulardii* *vs* placebo	89 adult outpatients on amoxicillin	1×10^{10} (500 mg)	12	9	3/41 (7.3)	5/45 (11.1)

[a]$P < 0.05$, probiotic *vs* controls. cfu: Colony forming unit; nr: Not reported; abx: Antibiotics.

L. acidophilus and *Bifidobacterium lactis* and found significantly fewer patients developed AAD in only the *S. boulardii* group (5%, $P = 0.05$) compared with placebo (30%). Cindoruk *et al*[42] also found a significant reduction in AAD in adult patients treated with triple therapy for *H. pylori* infections for those randomized to *S. boulardii* (14.5%, $P < 0.05$) compared with placebo (30.6%). None of these trials reported any adverse reactions associated with *S. boulardii*.

It is important to have a sufficiently long follow-up period (usually 4-6 wk after cessation of antibiotics) to capture delayed-onset AAD. Several studies have shown that AAD may occur in patients on antibiotics, but AAD may also be delayed for up to two months (in up to 38% of patients) after antibiotics are discontinued[54,129]. Most studies of AAD followed patients for 4-6 wk after antibiotic treatment to document delayed-onset AAD[42,44,135]. In contrast, Lewis *et al*[133] found no significant reduction in AAD in a study of 69 elderly patients randomized to 226 mg of *S. boulardii* (4.5×10^9 cfu/d) or placebo for 14 d. This failure may have been due to a flawed study design, in that patients were only followed while on antibiotics and no follow-up was done after antibiotics were discontinued. The study by Lewis *et al*[133] therefore, may have missed a significant number of AAD cases due to a too short follow-up period. Short or no follow-up after antibiotic exposure may explain why some studies[133,136] did not find a significant protective effect of *S. boulardii*[137]. No adverse reactions associated with *S. boulardii* were noted in any of these studies. No other strains of Saccharomyces have been found to be effective to prevent AAD.

Meta-analyses for AAD: The literature search yielded 322 unique citations on *S. boulardii*, of which 278 were excluded: non-*S. boulardii* studies ($n = 19$), reviews ($n = 84$), pre-clinical studies including animal models of efficacy, mechanism of action, *in vitro* assays or strain characterization ($n = 130$), case reports or case series ($n = 15$), and phase Ⅱ safety or pharmacokinetic studies ($n = 30$). Of the 44 randomized controlled trials with *S. boulardii* screened, 34 were excluded (pediatric populations, $n = 17$; or non-AAD indications in adults, $n = 17$) and 10 were included (AAD in adult populations). As significant heterogeneity was found among studies, a random effect model was used. The random effect model gave a $\chi^2 = 10.8$, $P = 0.29$, indicating that the heterogeneity was well controlled. A meta-analysis of the ten randomized, controlled trials in adults presented in this review found that *S. boulardii* was significantly protective for AAD (Figure 3), with a pooled relative risk of 0.47 (95% confidence interval 0.35-0.63, $P < 0.001$). Begg's test did not find any significant publication bias ($P = 0.93$), nor did the funnel plot (data not shown). The number needed-to-treat (NTT) to prevent one case of AAD was 10.2.

In the established medical literature, meta-analysis has been used to combine different probiotic strains and studies to obtain a pooled estimate of the efficacy of probiotics for the prevention of AAD. A note of caution, however, while most meta-analyses have concluded that probiotics are effective for preventing AAD[123,138], it is inappropriate to conclude that all probiotic strains are effective. The effectiveness of probiotics is strain-specific and disease-specific, so each probiotic strain must be linked to the disease. Most probiotic meta-analyses have focused on one type of disease indication with a variety of probiotic strains (e.g. antibiotic associated diarrhea)[123,138,139]. When there are sufficient numbers of clinical trials, a meta-analysis limited to one disease indication and one type of probiotic strain may reduce the heterogeneity of studies[140]. Szajewska *et al*[141] limited her meta-analysis to randomized controlled trials of one type of probiotic (*S. boulardii*) in adults and children.

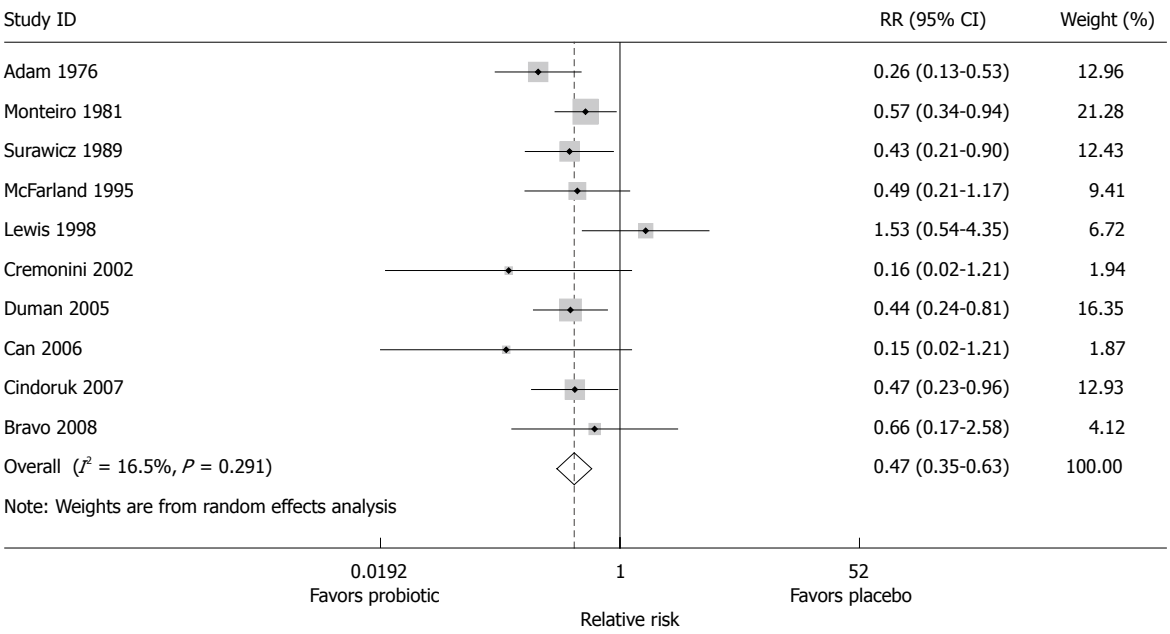

Figure 3 Forest plot of meta-analysis of ten randomized controlled trials measuring protective effect after treatment with *S. boulardii* or placebo for the prevention of antibiotic-associated diarrhea in adult patients. The x-axis depicts effect size, with black dot denoting the relative risk and the line indicating 95% CI, with the size of the grey box proportional to the study size. Relative risks to the left of RR = 1 denote study favored the probiotic, RR to the right denotes the study favors the placebo. Overall, pooled RR was 0.47 (0.35-0.63).

Pooling the results 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). As an alternative, some meta-analyses have done sensitivity analysis, separating out sub-groups by patient type (e.g. just adults or just children) or by type of probiotic strain[123,142]. One sensitivity analysis found with sufficient evidence that only two probiotic strains had significant efficacy for the prevention of AAD, i.e. *S. boulardii* and *L. rhamnosus* GG. However, *L. rhamnosus* GG probiotics may be contraindicated that this strain is susceptible when the patient is prescribed a type of antibiotic[123]. Although many meta-analyses have been done, pooling studies must be performed with these limitations in mind.

CDI

Epidemiology of *C. difficile* disease: For over two decades, *Clostridium difficile* infections continue to persist as a leading cause of nosocomial gastrointestinal illness[143-146]. The incidence rates of CDI have been increasing globally. In the US, CDI doubled to 301 200 cases from 2001 to 2005[147]. It is estimated that 450 000-750 000 CDI cases will occur per year by 2010 in the US[148,149]. Outbreaks of an emergent strain, BI/NAP1/027, caused large outbreaks of severe CDI with a high mortality rate in Canada between 2003-2005[150]. Studies have documented that CDI extends patients' hospital stays from 4 to 36 d[151-154]. In a study of 1034 CDI cases in Massachusetts in 2000, the average cost ranged from $10 212-$13 675/patient[155], leading to a nation-wide cost of $3.2 billion/year for CDI. There are only two standard antibiotics for CDI (vancomycin and metronidazole) and the response rate of metronidazole has been declining[152]. In addition, 20%-60% of patients may develop recurrent episodes of CDI despite additional antibiotic treatment. Although other investigational antibiotics are under development, no new antibiotics are superior to the two standard antibiotics.

Efficacy evidence for *C. difficile* disease: Probiotics may offer promise as an adjunctive therapy (given along with standard antibiotics vancomycin or metronidazole) for CDI. A meta-analysis of six randomized controlled trials of different probiotics (*S. boulardii*, *Lactobacillus rhamnosus* GG, *L. planatarum* 299v, and a mix of *L. acidophilus* and *Bifidobacterium bifidum* showed probiotics, in general, had a overall significant efficacy to prevent subsequent recurrences of *C. difficile* disease (RR = 0.59, 95% CI: 0.41-0.85, P = 0.005)[123]. However, due to limited number of trials, no meta-analysis was conducted for one probiotic strain.

S. boulardii shows promise for *C. difficile* infection control at several levels: it produces a 54-kDa serine protease that directly degrades *Clostridium difficile* toxins and also directly destroys the colonic receptor site for *C. difficile*[76], *S. boulardii* increases the immune response to *Clostridium difficile* toxins A and B[108], and animal models of *C. difficile* disease respond to this yeast. In addition, case reports or small case series of patients with recurrent *C. difficile* diarrhea treated with *S. boulardii* showed improvement. Toothaker and Elmer found that significantly fewer (51%) hamsters challenged with *C. difficile* died if given *S. boulardii* (5% solution) compared with the saline controls (80%)[156]. Subsequent studies confirmed this efficacy in other animal models: gnotobiotic mice[41,157,158], rats[89,103], and turkeys[159]. Since 1989, case reports or small case series have reported that patients with recurrent CDAD were either cured or improved by *S. boulardii* treatment[40,59, 160,161].

Table 3 Randomized controlled trials for the treatment of *C. difficile* disease using *S. boulardii*

Ref.	Treatment groups	Study population	Daily dose: cfu/d (mg/d)	Duration of treatment (wk)	Follow-up (wk)	*C. difficile* recurrence in probiotic group	*C. difficile* recurrence in placebo group
McFarland *et al*[53]	*S. boulardii vs* placebo	124 adult patients on varied doses of vancomycin or metronidazole; recurrent and initial CDAD cases; 3 referral sites, US	3×10^{10} (1000 mg)	4	4	15/57 (26.3%)[a]	30/67 (44.8%)
Surawicz *et al*[60]	*S. boulardii vs* placebo	168 adult patients recurrent CDAD; on vancomycin (2 g/d, $n = 32$) or V (500 mg/d, $n = 83$) or M (1 g/d, $n = 53$); 4 referral sites, US	2×10^{10} (1000 mg)	4	4	V (2 g/d) 3/18 (17%)[a]; V (500 mg/d) 23/45 (51%); M (1 g/d) 13/27 (48.1%)	V (2 g/d) 7/14 (50%); V (500 mg/d) 17/38 (44.7%); M (1 g/d) 13/26 (50%)

[a]$P < 0.05$, probiotic *vs* controls. V: Vancomycin; M: Metronidazole.

There was a case report[162] and two small case series with 3-4 patients[163,164] with recurrent *C. difficile* disease who seemed to have responded to *S. cerevisiae* administration. However, since no comparison groups or controls were used, there is no foundation to claim the efficacy of other strains of Saccharomyces for *C. difficile* disease.

There have been two randomized, double blinded, controlled trials for the use of *S. boulardii* and antibiotics for patients with recurrent *C. difficile* disease (Table 3)[53,60]. In a multisite, randomized, double-blinded, placebo-controlled trial of 168 patients with recurrent *C. difficile* disease, standard antibiotics were combined with *Saccharomyces boulardii* or placebo[60]. Three antibiotic regimens were used for 10 d: either high-dose vancomycin (2 g/d), low-dose vancomycin (500 mg/d) or metronidazole (1 g/d). Then either *S. boulardii* or placebo (1 g/d for 28 d) was added to the antibiotic treatment. The patients were followed up for two months for subsequent *Clostridium difficile* recurrences. A significant decrease in recurrences was observed only in patients treated with the high-dose vancomycin and *S. boulardii* treatment (16.7%) compared with patients who received high-dose vancomycin and placebo (50%, $P = 0.05$). There were no significant reductions in recurrence rates in either the low-dose vancomycin or metronidazole treatment group, regardless if *S. boulardii* was used. No serious adverse reactions were noted in any of these patients. By the end of the antibiotic treatment, only high-dose vancomycin completely cleared *C. difficile* toxin from the colon, low-dose vancomycin and metronidazole could not clear the toxin. A subsequent investigation of 163 patients with recurrent CDI confirmed this finding[165]. In this study, stool samples were assayed at the end of antibiotic treatment to determine if there was a difference in toxin clearance by the type or dose of antibiotic. Treatment with high-dose (2 g/d) of vancomycin completely cleared *C. difficile* toxin, but 11% of those treated with lower doses of vancomycin and 41% treated with metronidazole were positive for *C. difficile* at the end of antibiotic treatment. *S. boulardii* may be more effective if complete *C. difficile* toxin clearance is achieved before sole reliance upon the yeast probiotic is required.

An earlier randomized, controlled double-blinded study had also found efficacy of the combination treatment using a standard antibiotic (vancomycin or metronidazole) and *S. boulardii* for patients with *C. difficile* disease[53]. This study did not control the dose or duration of either vancomycin or metronidazole (it was under the physician's discretion), but randomized patients to either *S. boulardii* (1 g/d) or placebo for 28 d. All patients were followed up for two months for subsequent recurrences. Approximately half of the enrolled patients had their first episode and half had recurrent *C. difficile* disease. Twenty-six percent of the 57 patients given *S. boulardii* had a recurrence of *C. difficile* disease, which was significantly fewer as compared with 45% of the 67 given placebo ($P < 0.05$). The strongest effect was found in the 60 patients with recurrent *C. difficile* disease; significantly fewer patients (35%) given *S. boulardii* had a recurrence compared with 65% of patients given placebo ($P = 0.04$). Two adverse reactions were associated with *S. boulardii* (thirst and constipation). No randomized controlled trials using stains of *S. cerevisiae* for this disease were found in the literature.

H. pylori

Epidemiology of *H. pylori*: *H. pylori* colonizes the gastric mucosa and usually induces a chronic, asymptomatic carrier state, but some people may develop gastroduodenal ulcers as a result. Carriage of *H. pylori* is a risk factor for developing gastric lymphoma or adenocarcinoma in later life. The prevalence of *H. pylori* carriage is 50%-80% worldwide[166,167]. Standard treatment for *H. pylori* involves a two-week course of triple therapy (usually clarithromycin, amoxicillin and an acid suppressor such as lansoprazole or omeprazole), that also has gastrointestinal side effects.

Efficacy for *H. pylori*: *S. boulardii* induces morphologic changes in *H. pylori* cells consistant with cellular damage[21] and was shown to reduce 12% of *H. pylori* colonization in infected children in one trial[46]. Of four randomized controlled trials testing *S. boulardii* in *H. pylori* infections, two were in children[46,168] and two (Table 4) were in adults[42,134]. Cremonini *et al*[134] first explored the efficacy of probiotics to eradicate *H. pylori* in 85 asymptomatic carriers. They

Table 4 Randomized, controlled trials for acute disease conditions using *S. boulardii*

Ref.	Treatment groups	Study population	Daily dose: cfu/d (mg/d)	Duration of treatment	Follow-up (wk)	Outcome in probiotic	Outcome in controls
	Helicobacter pylori						
Cremonini *et al*[134]	*S. boulardii* (Codex, SmithKine Beecham, Italy) *vs* placebo *vs* LGG *vs* mix (*L acid* and *Bifid lactis*)	85 asymptomatic carriers *H. pylori* 22 SB and 21 placebo; all received triple therapy	5×10^9 (nr)	2 wk	2	Eradicated in: 17/21 (81%) same for LGG and mix Any symptoms: 4/21 (19%)[a]	Placebo, 16/20 (80%) Any symptoms: 12/20 (60%)
Cindoruk *et al*[42]	*S. boulardii* (Reflor, Turkey) *vs* placebo	124 adults with *H. pylori* dyspepsia, all received triple therapy	2×10^{10} (1000 mg)	2 wk	6	Eradication 44/62 (71%) Epigastric distress: 9 (14.5%)[a]	Eradication 37/62 (59.7%) Distress: 27 (43.5%)
	Acute adult diarrheas						
Hochter *et al*[169]	*S. boulardii* *vs* placebo	92 German outpatient adults	8×10^9 (300-600 mg)	8 d	0	Diarrhea score reduction: -17.2 + 6.8[a]	Score: -13.6 + 8.7
Mansour-ghanaei *et al*[51]	*S. boulardii* (UltraLevure, France) *vs* placebo. Both groups got metro and lodoquinol	57 enrolled, 54 done; adults with *E. histolytica* amoebic dysentery	1.5×10^{10} (750 mg)	10 d	4	Cured: 27/27 (100%)[a]	Cured: 5/27 (19%)
	Enteral feeding-related diarrhea						
Tempe *et al*[61]	*S. boulardii* *vs* placebo	40 adults in ICU	1×10^{10} (nr)	11-21 d	0	34/389 days of diarrhea (8.7%)[a]	63/373 days of diarrhea (16.9%)
Schlotterer *et al*[171]	*S. boulardii* *vs* placebo	20 enrolled, 18 done, burnt adults 18-70 yr	4×10^{10} (2000 mg)	8-28 d	0	3/204 days of diarrhea (1.5%)[a]	19/208 days of diarrhea (9.1%)
Bleichner *et al*[39]	*S. boulardii* *vs* placebo	131 enrolled, 128 done, adults in ICU	4×10^{10} (2000 mg)	3 wk	0	50/648 days of diarrhea (7.7%)[a]	87/683 days of diarrhea (12.7%)
	Traveler's diarrhea						
Kollaritsch *et al*[175]	*S. boulardii* *vs* placebo	832 Austrian tourists to hot climates	2×10^9 (250 mg)	5 d before trip and mean 21 d trip	0	143/426 (34%)[a]	173/406 (43%)
Kollaritsch *et al*[175]	*S. boulardii* *vs* placebo	805 Austrian tourists to hot climates	5×10^9 (500 mg)	5 d before trip and mean 21 d trip	0	127/399 (32%)[a]	173/406 (43%)
Kollaritsch *et al*[49]	*S. boulardii* *vs* placebo	713 Austrian tourists to hot climates	2×10^9 (250 mg)	5 d before trip and mean 21 d trip	0	121/352 (34%)[a]	141/361 (39%)
Kollaritsch *et al*[49]	*S. boulardii* *vs* placebo	664 Austrian tourists to hot climates	2×10^{10} (1000 mg)	5 d before trip and mean 21 d trip	0	87/303 (29%)[a]	141/361 (39%)
Bruns *et al*[176]	*S. cerevisiae* Hansen (CBS 5926) *vs* active treatment[1]	60 tourists in Tunisia with traveler's diarrhea, 43 done	1.0×10^{10} (600 mg)	5 d	0	Duration diarrhea 2.1 d	1.4 days of diarrhea[a]

[a]$P < 0.05$, probiotic *vs* controls; [1]Strain currently known as *S. boulardii*.

randomized patients to one of three probiotic treatments (*S. boulardii*, *L. rhamnosus* GG or a mixture of *L. acidophius* and *Bifidobacterium lactis*) or placebo for 14 d. All patients were treated with the triple therapy for the first week. By the end of the second week, eradication rates were similar for all groups (81% for *S. boulardii vs* 80% of placebo). A promising result of this study was a lower rate of antibiotic-associated diarrhea (5%) in all the probiotic groups compared with 30% of the placebo group. A subsequent study by Cindoruk *et al*[42] assessed *S. boulardii* for both eradication of *H. pylori* and the reduction of side-effects of the standard triple treatment. This study enrolled 124 adults with *H. pylori* dyspepsia in Turkey who were receiving the triple therapy and randomized to either 1 g of *S. boulardii* (2×10^{10}/d for 2 wk) or placebo. Patients were followed up for six weeks for side-effects and *H. pylori* clearance. Although there was no significant difference in *H. pylori* eradication (71% in *S. boulardii vs* 60% in placebo), significantly fewer patients randomized to *S. boulardii* reported epigastric distress (14.5%, $P < 0.05$) compared with placebo (43.5%), as well as lower global dyspepsia symptom scores. The frequency of AAD was also significantly reduced in those receiving *S. boulardii* (14.5%) compared with the placebo group (30.6%). These studies indicate that *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.

Acute adult diarrheas

Epidemiology of acute adult diarrhea: Acute adult diarrhea is a broad classification for diarrhea that includes illnesses that may develop quickly, but are typically short-lived and are sporadic. The etiologies of acute adult diarrhea may include infectious agents (*Entamoeba histolytica*, *E. coli*, or Salmonella) or may be idiopathic. Diarrhea in adults occurring in outbreaks or due to other situations (antibiotic-associated diarrhea, *C. difficile*-associated diarrhea, traveler's diarrhea, inflammatory bowel disease or irritable bowel disease) are not included in this classification.

Clinical efficacy for acute adult diarrhea: Two randomized controlled trials using *S. boulardii* showed that this probiotic may be effective in treating acute diarrhea due to a variety of causes. Hochter *et al*[169] enrolled 92 German

adult outpatients with acute diarrhea and randomized them to *S. boulardii* (8×10^9/d) or placebo for eight days. By the third day, the 43 given *S. boulardii* had a significantly lower diarrhea severity score (5.5 ± 6.8, $P = 0.04$) compared with the 49 given placebo (6.7 ± 8.7). Mansour-Ghanaei *et al*[51] enrolled 57 patients with acute *Entamoeba histolytic* dysentery and treated them with *S. boulardii* (1.5×10^{10}/d for 10 d) or nothing (control). Both groups also received metronidazole and iodoquinol for 10 d. At the end of four weeks, all the patients given *S. boulardii* were cured compared with 19% of those not given the yeast. Unfortunately, the number of trials in this area is small and the etiologies were different in the two trials, so conclusions are limited. No randomized controlled trials using stains of *S. cerevisiae* for this disease were found in the literature.

Enteral nutrition-related diarrhea

Epidemiology of enteral nutrition-related diarrhea: Diarrhea is a common complication associated with enteral tube feeding and may result in a loss of nutrition in an already seriously ill patient. The frequency of diarrhea in enteral tube fed patients has been reported as high as 50%-60%[170] and complications may include life-threatening acidosis, increased morbidity and mortality and increased healthcare costs. Schneider *et al*[102] reported a significant increase in short-chain fatty acids in 10 enteral-fed patients receiving *S. boulardii* (1 g/d for 6 d) compared with 15 healthy controls.

Clinical efficacy for enteral nutrition related diarrhea: Three randomized, controlled trials have assessed the ability of *S. boulardii* to reduce diarrhea in patients receiving this type of nutritional intake (Table 4). Tempe *et al*[61] compared 40 enteral-fed patients randomized to either *S. boulardii* (1×10^{10}/d) or placebo for 11-21 d and found significantly fewer patients (8.7%) given *S. boulardii* developed diarrhea compared with placebo (16.9%). Schlotterer *et al*[171] randomized 18 patients with burns who were receiving enteral nutrition to *S. boulardii* (4×10^{10}/d) or placebo for 8-28 d. Those given *S. boulardii* suffered fewer diarrhea days (3/204 d, 1.5%) than those given placebo (19/208 d, 9.1%, $P < 0.001$). The efficacy of *S. boulardii* was confirmed in a later study of 128 intensive care unit (ICU) patients randomized to either *S. boulardii* (4×10^{10}/d) or placebo for 21 d[39]. Those given *S. boulardii* reported significantly fewer diarrheal days (7.7%) than those given placebo (12.7%). No adverse reactions associated with *S. boulardii* were reported in any of these three trials.

Traveler's diarrhea

Epidemiology of traveler's diarrhea: Traveler's diarrhea (TD) is a common health complaint among travelers; globally 12 million cases are reported every year[172]. Rates of TD range from 5% to 50%, depending upon the destination, with equatorial countries having the highest rates of TD. TD usually occurs as sporadic cases, but outbreaks of TD may occur in large groups traveling or located together (tourists on cruise ships, group tours, military personnel, disaster-relief groups). The etiologies of TD vary widely, but commonly include enterotoxigenic and entroaggregative *E. coli*, *Campylobacter jejuni*, *Salmonella typhimurum*, viruses (Norwalk or Rotavirus) or parasites (*Entamoeba histolytica*, *Giardia lamblia*). Traditional preventive measures including frequent handwashing, avoiding high-risk foods and water and ingestion of bismuth subsalicyclate showed only modest protection[173].

Clinical efficacy for TD: A meta-analysis of 12 randomized, controlled trials of various probiotics (including *S. boulardii*, *Lactobacilli* and mixtures of different probiotic strains) for the prevention of TD found a significant reduction in the risk of TD if probiotics were used (RR = 0.85, 95% confidence interval 0.79-0.91)[174]. Two randomized controlled trials have been done with *S. boulardii* that included a total of four different probiotic treatment arms (Table 4). Kollaritsch *et al*[175] enrolled 1231 Austrian tourists traveling to hot climates and randomized travelers to either of two doses of *S. boulardii* (250 or 500 mg/d) or placebo for 3 wk. The treatment was started 5 d prior to the trip and continued through the duration of the trip. Traveler's diarrhea developed in 43% given placebo and significantly fewer in those given the low-dose *S. boulardii* (34%) and the higher dose *S. boulardii* (32%). A second study by Kollaritsch *et al*[49] was done with 3000 Austrian tourists traveling to northern African, the Middle East and the Far East. Travelers were randomized to either 250 mg/d (5×10^9) *S. boulardii*, 1000 mg/d (2×10^{10}) *S. boulardii* or placebo, starting five days before leaving and throughout the duration of their trip (median of 3 wk). Only 1016 (34%) completed the study, but *S. boulardii* significantly reduced the incidence of traveler's diarrhea in a dose-dependent manner. Of the travelers given placebo, 39% developed diarrhea whereas only 34% of those given the lower dose and 29% of those given the higher dose of *S. boulardii* developed traveler's diarrhea ($P < 0.05$). No adverse reaction was noted by the travelers in either of these studies.

Bruns *et al*[176] tested *S. cerevisiae* Hansen CBS 5926 (Perenterol®, Germany) to treat travelers who had developed TD in Tunisia. Travelers with TD were randomized to 600 mg of *S. cerevisiae* (1×10^{10}/d) for five days or an active control treatment and the duration of their TD tracked. Of 60 enrolled, 43 completed the trial, but the duration of diarrhea was not significantly different between those given *S. cerevisiae* (2.1 d) and those given ethacridine-lactate and tannalbuminate (1.4 d). This strain is known as *S. boulardii* outside of Germany. No other randomized controlled trials have been done for the treatment of TD using *S. boulardii*. These limited numbers of studies indicate that probiotics may be more effective in preventing TD, rather than treating the diarrhea once it becomes symptomatic.

CLINICAL EFFICACY: CHRONIC DISEASES

S. boulardii has been tested for clinical efficacy in several types of chronic diseases including Crohn's disease, irri-

table bowel syndrome, giardiasis and human immunodeficiency virus (HIV)-related diarrhea.

Inflammatory bowel disease

Epidemiology of inflammatory bowel disease: inflammatory bowel diseases (IBDs) are chronic, immune-related inflammatory diarrheas, which include ulcerative colitis, pouchitis and Crohn's disease. The incidence of Crohn's disease varies by countries, with the highest incidences (8-66/100 000) found in Wales, New Zealand, Canada, Scotland, France, Netherlands, intermediate rates (4-7/100 000) in UK, USA, Europe, Australia, and the lowest rates (0.2-3/100 000) in South America, China, Korea, Japan[177]. In Crohn's disease, typically the lower small intestine and colon are the most affected organs. Symptoms include diarrhea, abdominal pain or cramping and loss of appetite. Unlike ulcerative colitis, lesions of Crohn's disease are deep and patchy and often involve thickened areas resulting in intestinal obstruction, which can be life threatening. Disruption of the intestinal wall also allows intestinal bacteria to translocate and incite the immune system. Complications of Crohn's disease are common, in that 40% of Crohn's patients report lower GI bleeding, intestinal obstruction, or perforation[178]. Lifetime risk for surgery in Crohn's patients is extremely high (70%-80%)[179]. Unfortunately, the cause of Crohn's disease is not known, so current therapies are directed at symptom relief. But 10%-60% suffer recurrences of Crohn's disease after treatment is completed[180].

Clinical efficacy for IBD: Guslandi *et al*[48] enrolled 25 adults with mild to moderate ulcerative colitis in a pilot study and treated them with a combination of mesalazine (3 g/d) and *S. boulardii* (1.5×10^{10}/d) for 4 wk. All of these patients had histories of poorly tolerated steroid courses. Most (68%) of the patients responded to the probiotic treatment. This study had a promising result, but the implications were uncertain as patients treated for only a short time, were not followed up for subsequent flare-ups of their disease and there was no control group in this pilot study. Garcia Vilelea *et al*[62] enrolled 31 patients with Crohn's disease in remission (at the time of enrollment). All patients continued their maintenance medications during the trial (mesalamine, azathioprine or others). Patients were randomized to either *S. boulardii* (2×10^{9}/d) for three months or placebo. 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 translocation in these patients.

Two randomized controlled clinical trials have been done testing *S. boulardii* for patients with Crohn's disease (Table 5)[47,57]. Plein *et al*[57] randomized 20 patients with Crohn's disease to either 750 mg of *S. boulardii* (1.5×10^{10}/d) or placebo for seven weeks. All patients continued their maintenance medications during the trial. At the end of seven weeks, patients treated with *S. boulardii* were significantly improved (mean = 3.3 ± 1.2 stools/d, $P < 0.05$) compared with the placebo group (mean = 4.6 ± 1.9 stools/d). Guslandi *et al*[47] studied the effect of *S. boulardii* on the rate of Crohn's disease relapses in a study of 32 patients with Crohn's disease in Italy. Adults (23-49 years old) who were in remission were randomized to either 1 g of *S. boulardii* (2×10^{10}/d) and mesalamine (2 g/d) or mesalamine alone (3 g/d) for 6 mo. Significantly fewer patients treated with *S. boulardii* (6%, $P = 0.04$) relapsed than the control group (38%). No adverse reactions associated with *S. boulardii* were reported in any of these trials.

Crohn's disease is a challenging condition for clinical trials in that it is sporadic, has no defined etiology, has multiple measurable disease outcome and requires lengthy treatment and follow-up period. *S. boulardii* offers promise to this group of patients who are in need of a safe and effective therapy for this chronic condition. The probiotic protection seems to be strain specific. A study tested another strain of *S. cerevisiae* (Baker's yeast) in 19 adults with Crohn's disease, but found the disease was worse in those receiving this strain than in controls[181].

Irritable bowel syndrome

Epidemiology of irritable bowel syndrome: Irritable bowel syndrome (IBS) is a frequent disorder characterized by a triad of symptoms (bloating, abdominal pain, and intestinal transit disturbances). The prevalence of IBS is high (3%-20%) in the general population and IBS may account for 25%-50% of gastroenterologist practice[182]. Consequences of IBS include worse quality of life[183], higher health care costs ($1.7 billion in health care costs)[184], and higher incidences of depression[185].

Clinical efficacy for IBS: Standard treatments target symptom relief, but have not been more effective than placebo. IBS is a recent focus of probiotic clinical trials. A meta-analysis of 20 randomized, controlled trials (with 23 treatment arms) including 1404 subjects found a pooled relative risk (RR) for improvement in global IBS symptoms in 14 probiotic treatment arms (RR = 0.77, 95% CI: 0.62-0.94)[36]. One of those trials (Table 5) randomized 34 patients with IBS to *S. boulardii* (9×10^{9}/d) or placebo for four weeks[52]. A significant decrease in the daily number of stools was found in the *S. boulardii* group and 87.5% of this group reported their IBS had improved compared with 72% of the placebo group ($P < 0.05$). No adverse reactions were noted in this trial. More trials using *S. boulardii* for IBS are required.

Giardiasis

Epidemiology of giardiasis: This condition is characterized by long lasting diarrhea with symptoms ranging from mild to severe diarrhea, weight loss, abdominal pain and weakness. The incidence may be high in developing countries such as Colombia (13%) and lower in developed countries such as Germany (12/100 000)[186,187]. It is also found in people enjoying outdoor hiking and camping who drink contaminated untreated water that appears clean.

Clinical efficacy for giardiasis: Besirbellioglu *et al*[38] randomized 65 adults with giardiasis in Turkey to either *S. boulardii* (1×10^{10}/d) or placebo for 10 d. Both groups

Table 5 Randomized, controlled trials for chronic disease conditions using *S. boulardii*

Ref.	Treatment groups	Study population	Daily dose: cfu/d (mg/d)	Duration of treatment and follow-up	Outcome in probiotic	Outcome in controls
	Crohn's disease					
Plein *et al*[57]	*S. boulardii* (Perenterol®) *vs* placebo	20 enrolled with Crohn's, 17 done, all on maintenance medications	1.5×10^{10} (750 mg)	7 wk	3.3 ± 1.2 stools/d at week 9[a]	4.6 ± 1.9 stools/d at week 9
Guslandi *et al*[47]	*S. boulardii* (Perenterol®) + mesalamine (2 g/d) *vs* mesalamine alone (3 g/d)	32 with Crohn's in remission in Italy (23-49 yr old)	2×10^{10} (1000 mg)	6 mo	1/16 (6%) relapse[a]	6/16 (38%) relapse
	Irritable bowel syndrome					
Maupas *et al*[52]	*S. boulardii vs* placebo	34 with IBS	9×10^{9} (nr)	4 wk	Mean decrease in #stools/d: -2.2/d[a] Improved: 14/16 (87.5%)[a]	Mean decrease -0.5/d Improved: 13/18 (72%)
	Giardiasis					
Besirbellioglu *et al*[38]	*S. boulardii* + metro (2250 mg/d) *vs* placebo + metro	65 adults with giardiasis	1×10^{10} (500 mg)	10 d with 4 wk f/up	100% cured, 0% giardia cysts[a]	100% cured 6/35 (17%) cysts present
	HIV-related diarrhea					
Saint- Marc *et al*[189]	*S. boulardii vs* placebo	35 French AIDS patients with chronic diarrhea	6×10^{10} (3000 mg)	7 d	11/18 (61%) cured[a]	2/17 (12%)

[a]$P < 0.05$, probiotic *vs* controls. IBS: Irritable bowel syndrome; HIV: Human immunodeficiency virus; AIDS: Acquired immune deficiency syndrome; f/up: Follow-up time.

also received metronidazole for the same duration. Two weeks later, both groups reported a resolution of their diarrhea, but none of those on *S. boulardii* had detectable giardia cysts, while significantly more (17%) on placebo still carried giardia cysts.

HIV diarrhea

Epidemiology of HIV-related diarrhea: Patients infected with HIV are susceptible to a variety of diseases and may also develop chronic life-threatening diarrhea. The prevalence of diarrhea in HIV patients ranges from 50%-60% in developed countries and nearly 100% in developing countries[188].

Clinical efficacy for HIV-related diarrhea: A blinded, placebo-controlled dose-ranging study was done in 11 HIV positive patients who had chronic diarrhea[45]. *S. boulardii* was given at 1-3 g/d and six patients reported diarrhea was controlled while taking 3 g/d after one month, while lower doses of *S. boulardii* were not as effective. Patients with HIV-associated diarrhea seem to be one group that requires a higher than typical dose of *S. boulardii*. Saint-Marc *et al*[189] randomized 35 Stage IV AIDS adult patients with chronic diarrhea to either *S. boulardii* (3 g/d or 6×10^{10}/d) or placebo for one week (Table 5). Significantly more of those given *S. boulardii* (61%, $P = 0.002$) had their diarrhea resolved compared with placebo (12%) patients. *S. boulardii* was well tolerated by all HIV patients even treated with high doses of 3 g/d in these two studies.

SAFETY OF *S. BOULARDII*

The use of a living organism as therapy increases the potential risk in four general areas: transfer of antibiotic-resistance genes, translocation of the living organism from the intestine to other areas of the body, persistence in the intestines and the development of adverse reactions. The first three theorical concerns are of minimal impact on *S. boulardii*. Unlike other bacterial strains of probiotics, such as *Enterococcus faecium* and *Lactobacillus rhamnosus*, which have been shown to acquire antibiotic-resistance genes, *S. boulardii* has not developed any antibiotic or antifungal resistance[190,191]. Data from animal models shows reduced translocation with *S. boulardii* treatment[64,89], unlike other strains of *S. cerevisiae*[192]. As pharmacokinetic studies indicate, *S. boulardii* does not persist 3-5 d after oral ingestion is discontinued, so persistence is not a concern for this probiotic[118].

S. boulardii has been used as a probiotic since the 1950s in Europe and has been investigated in clinical trials worldwide. Safety and adverse event data collected during clinical trials, when patients are closely monitored for problems associated with the investigational treatment, has documented a remarkable safety profile of *S. boulardii* in adults. A wide diversity of adult patients have been followed up who were either randomized to *S. boulardii* as part of a clinical trial or were documented in case series or case reports for various disease indications (TD, $n = 1596$; AAD, $n = 958$; adult acute diarrhea, 156; enteral tube feeding, $n = 103$; IBD, $n = 66$; IBS, $n = 16$, HIV-related diarrhea, $n = 18$ and giardia infections, $n = 50$). These studies provide safety data for a total of 2963 adult patients and the only adverse reactions associated with *S. boulardii* was thirst (in 5 patients) and constipation (in 8 patients) in a trial of patients with *C. difficile* infections[53]. No case of *S. boulardii* fungemia has been reported in these diverse patient populations enrolled in clinical trials.

Infrequent cases of fungemia have been reported in case reports or case series in the literature. Most of the adult cases of *S. boulardii* fungemia are with serious co-

Table 6 Summary of recommendations for clinical use of *S. boulardii* in adults

Use for disease	Dose (mg/d)	Duration	Adjunct to	Strength of evidence[1]
Prevention of antibiotic associated diarrhea	500-1000	During antibiotics with additional 3 d to 2 wk after	Nothing	++++
Prevention of Traveler's diarrhea	250-1000	Duration of trip (3 wk)	Nothing	+++
Enteral nutrition-related diarrhea	2000	8-28 d	Nothing	++
H. pylori symptoms	1000	2 wk	Standard triple therapy	++
Treatment of *Clostridium difficile* infections	1000	4 wk	Vancomycin or metronidazole	+
Acute adult diarrhea	500-750	8-10 d	Nothing	+
Inflammatory bowel disease	750-1000	7 wk to 6 mo	Mesalamine	+
Irritable bowel syndrome	500	4 wk	Nothing	+
Giardiasis	500	4 wk	Metronidazole	+
HIV-related diarrhea	3000	7 d	Nothing	+

[1]Strength of evidence, + (weak, needs more randomized controlled trials) to ++++ (strong, efficacy and safety are evidence based from numerous large randomized controlled trials).

morbidities and have central venous catheters. Most cases responded well to treatment with fluconazole or amphotericin B[193]. Some cases developed fungemia, not from the direct ingestion of *S. boulardii* probiotics, but acquired the yeast from contaminated environmental fomites[194]. Fungemia from *S. cerevisiae* (non-boulardii strains) have also been reported and are similar to *S. boulardii* cases, but have poorer prognosis[195,196]. A challenge to determining valid incidence of fungemia is the lack of available advanced yeast identification assays which can distinguish *S. cerevisiae* from *S. boulardii*.

CONTRAINDICATIONS/PRECAUTIONS

Even though fungemia with *S. boulardii* is infrequent, it may be prudent to closely follow up the adult inpatients who are severely ill or in intensive care units and have central catheter for episodes of unexplained fever. Some studies have recommended not to give *S. boulardii* to immunosuppressed patients or those with central catheters to reduce this risk[108].

Unlike many bacterial probiotics, there are few drug or antibiotic interactions with *S. boulardii*. However, if patients are on anti-fungal medications, a staggered dose regime (at least 4 h apart) is suggested[45].

CONCLUSION

The use of *S. boulardii* as a therapeutic probiotic is supported by its mechanisms of action, pharmacokinetics, and efficacy from animal models and clinical trials. The overall safety profile for *S. boulardii* is beneficial. *S. boulardii* can be recommended for several diseases. Other strains of Saccharomyces may have probiotic properties, but clinical efficacy evidence for other strains are still deficient. Guidelines for the most effective use of *S. boulardii* are given in Table 6 and generally, the daily dose is typically $> 10^9$/d, the duration of treatment can vary from 7 d to 6 mo and it may be given alone or as an adjunctive treatment, depending upon the disease indication. *S. boulardii* is significantly effective for the prevention of AAD and prevention of TD. Trials also show evidence for *S. boulardii* in the reduction of side-effects of *H. pylori* treatment and the prevention of enteral nutrition-related diarrhea. More clinical trials are encouraged for the treatment of chronic diseases (Crohn's disease, irritable bowel syndrome and HIV-related diarrhea) and the prevention of *C. difficile* disease recurrences.

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