

Prevention of *Clostridium difficile* infection with *Saccharomyces boulardii*: A systematic review

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BACKGROUND: *Clostridium difficile* is a major cause of antibiotic-associated diarrhea within the hospital setting. The yeast *Saccharomyces boulardii* has been found to have some effect in reducing the risk of *C difficile* infection (CDI); however, its role in preventive therapy has yet to be firmly established.

OBJECTIVE: To review the effectiveness of *S boulardii* in the prevention of primary and recurrent CDI. Benefit was defined as a reduction of diarrhea associated with *C difficile*. Risk was defined as any adverse effects of *S boulardii*.

METHODS: A literature search in MEDLINE, EMBASE, CINAHL and the Cochrane Library was performed. Included studies were English language, randomized, double-blind placebo controlled trials evaluating *S boulardii* in CDI prevention.

RESULTS: Four studies were reviewed. Two studies investigated the prevention of recurrence in populations that were experiencing CDI at baseline. One trial showed a reduction of relapses in patients experiencing recurrent CDI (RR=0.53; P<0.05). The other demonstrated a trend toward reduction of CDI relapse in the recurrent treatment group of patients receiving high-dose vancomycin (RR=0.33; P=0.05). Two other studies examined primary prevention of CDI in populations that had been recently prescribed antibiotics. These studies lacked the power to detect statistically significant differences. Patients on treatment experienced increased risk for thirst and constipation.

CONCLUSION: *S boulardii* seems to be well tolerated and may be effective for secondary prevention in some specific patient populations with particular concurrent antibiotic treatment. Its role in primary prevention is poorly defined and more research is required before changes in practice are recommended.

Key Words: *C difficile* infection; *Saccharomyces boulardii*; Probiotic

Clostridium difficile is a Gram-positive, spore-forming anaerobe that has been shown to be a major cause of antibiotic-associated diarrhea (AAD) within the hospital setting. *C difficile* infection (CDI) leads to a range of sequelae ranging from abdominal discomfort to fulminant pseudomembranous colitis (1). It is implicated in approximately 25% of all AAD cases, 50% to 75% of all antibiotic-related colitis cases and contributes significantly to morbidity in nosocomial populations (2). Mortality can result from complications of toxic megacolon and intestinal perforation (3). Recent reports of increases in CDI-related case fatality rates suggest the possibility of the circulation of highly virulent strains (4).

La prévention de l'infection par le *Clostridium difficile* au moyen du *Saccharomyces boulardii* : Une analyse systématique

HISTORIQUE : *Clostridium difficile* est une cause majeure de diarrhée associée aux antibiotiques en milieu hospitalier. La levure *Saccharomyces boulardii* s'est révélée capable d'exercer un certain effet en réduisant le risque d'infection à *C. difficile* (ICD). Par contre, son rôle en traitement préventif n'a pas encore été confirmé.

OBJECTIF : Passer en revue l'efficacité de *S. boulardii* dans la prévention de l'ICD primaire et récurrente. L'avantage était défini par une réduction de la diarrhée associée à *C. difficile*. Le risque était défini par tout effet indésirable de *S. boulardii*.

RÉSULTATS : Quatre études ont été passées en revue. Deux études portaient sur la prévention des récurrences dans des populations déjà porteuses d'ICD au départ. L'une a fait état d'une réduction des rechutes chez les patients qui présentaient des ICD récurrentes (RR = 0,53, P < 0,05). L'autre a fait état d'une tendance à réduire les récurrences d'ICD dans le groupe sous traitement qui recevait de la vancomycine à dose élevée (RR = 0,33, P = 0,05). Deux autres études se sont penchées sur la prévention primaire de l'ICD dans des populations à qui on venait de prescrire des antibiotiques. Cette étude n'était pas dotée de la puissance statistique nécessaire pour déceler des différences statistiquement significatives. Les patients traités ont été exposés à un risque accru de soif et de constipation.

CONCLUSIONS : *S. boulardii* semble bien toléré et pourrait être efficace en prévention secondaire chez certaines populations de patients spécifiques prenant concomitamment une antibiothérapie particulière. Son rôle en prévention primaire est mal défini et il faudra approfondir la recherche avant de pouvoir recommander un changement dans les pratiques.

Although most episodes respond to metronidazole or vancomycin therapy, recurrence of CDI after treatment occurs in up to 20% of all patients within four weeks and may be secondary to *C difficile* spores that persist in spite of the presence of high intraluminal antibiotic concentrations (2). Residual spores can germinate in the absence of antibiotic at the end of treatment (2). Another reason for relapse may be reinfection because the patient's environment may be contaminated with the organism's spores (5).

The yeast *Saccharomyces boulardii* was found to have some effect in reducing the risk of CDI and other gastrointestinal conditions such as traveller's diarrhea and AAD. *S boulardii*

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has been used widely in Europe for the prevention of AAD. Because it is generally not absorbed systemically, adverse effects are rare (5). The mechanism of action of *S. boulardii* has not been fully established. It may secrete a protease, which, in turn, binds to toxin A receptors, thus decreasing enterotoxin effects (5). Another proposed explanation is the release of secretory immunoglobulin A by the host, resulting in an immunoprotective effect that stimulates chloride absorption and activates reticuloendothelial and complement systems, and alleviates CDI symptoms in humans (5). A combination of these effects may also account for the reduction in the development of CDI.

The use of the probiotic has been controversial because there have been case reports of fungemia in both immunocompromised and immunocompetent patients. The reports also suggest increased risk for fungemia in patients with central venous catheters and the critically ill (6). These patients, however, are at higher risk of developing CDI and its associated complications. Therefore, this patient population may benefit from preventive therapy.

The present article reviews the literature pertaining to the effectiveness of *S. boulardii* for the prevention of CDI and the prevention of CDI recurrence.

METHODS

Search strategy

A literature search in MEDLINE (from August 1966 to January 2004), EMBASE (from 1980 to 2004 [week 36]), CINAHL (1982 to August 2004 [week 4]) and the Cochrane Library was performed. Search terms were: ("Double-Blind Method" [MeSH] OR "Randomized Controlled Trials" [MeSH] OR "Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trials" [MeSH] OR "Controlled Clinical Trial" [Publication Type] OR "Comparative Study" [MeSH] OR "Placebos" [MeSH] OR "rct" [tw] OR "Random Allocation" [MeSH] OR "controlled clinical trials" [MeSH] OR "clinical trials, phase II" [MeSH] OR "clinical trials" [MeSH] OR "clinical trials, phase I" [MeSH] OR "clinical trials, phase IV" [MeSH] OR "clinical trials, phase III" [MeSH]) AND ("Saccharomyces" [MeSH] OR "Probiotics" [MeSH] OR "saccharomyces" [tw] OR "Yeast, Dried" [MeSH] OR "florastor" [tw] OR "boulardii" [tw]) AND ("Clostridium Infections" [MeSH] OR "Clostridium" [MeSH] OR "clostridium difficile" [tw] OR "Diarrhea" [MeSH] OR "Colitis" [MeSH] OR "pseudomembranous colitis" [MeSH] OR "Enterocolitis, Pseudomembranous" [MeSH]). References cited in review articles and articles that met inclusion criteria were also manually examined for any further relevant articles. Manufacturers of *S. boulardii* probiotics were contacted as a reference source for clinical studies, but the studies provided were duplications of those identified in the initial literature search.

Study selection

Inclusion criteria were English language publications and human clinical trials. All studies that addressed the effect of *S. boulardii* in adult patients for preventing primary or recurring CDI were included. Trials that were nonrandomized, not written in English, were review articles or animal studies were excluded. In addition, a trial was excluded if it did not examine clinical end points such as onset of diarrhea, and did not directly test for the presence of *C. difficile* either by microbiological culture or detection of toxins A or B.

Data extraction

Data extraction was performed using a structured chart to ensure consistent, objective appraisal of all studies. Specific criteria included study design, population sample size, outcomes, interventions, measurement of outcomes and results.

Assessment of study quality and data analysis

Benefit was defined as a reduction in *C. difficile*-associated diarrhea, while risk was attributed to the adverse effects of *S. boulardii* treatment. Studies were assessed by examining the duration of follow-up and intention to treat analysis. Studies were then divided into two groups for analysis based on their examination of primary or secondary prevention. One group involved patients who were currently experiencing confirmed CDI, the other was comprised of patients who had been newly prescribed antibiotics without any signs or symptoms of *C. difficile* at baseline. Data analysis was performed both quantitatively and qualitatively. Quantitative data was summarized using absolute risk and OR calculated by Cochrane Collaboration Review Manager software. Results were examined for outcome measurements and statistical significance, which included 95% CIs.

RESULTS

The literature search resulted in a total of 283 citations. A number of articles were excluded for the following reasons: use of *S. boulardii* for other indications (n=97), use of other probiotics or drugs (n=44), animal studies (n=7), nontrial study (eg, reviews [n=76]), studies involving children or infants (n=29), languages other than English (n=21) and studies that did not use diarrhea as a clinical outcome (n=2). Further manual examination of references in both review articles and studies that met inclusion criteria resulted in the addition of one study. The selection process produced seven unique citations: five randomized controlled trials, one open-label, before and after study, and an open-label case series (2,3,7-11).

Five prospective, randomized, double-blind, placebo-controlled studies using parallel group designs were evaluated. One study was excluded at the data extraction stage because it did not compare the treatment and control groups in patients who experienced diarrhea and had a positive *C. difficile* assay, but instead, analyzed each outcome independently (8). Overall, four trials that analyzed the use of *S. boulardii* for the primary and secondary prevention of CDI were included and are summarized in Table 1 (3,9-11). The trials conducted by McFarland et al (3) and Surawicz et al (9) involved patient populations who were currently experiencing active diarrhea and had a positive *C. difficile* culture. Recurrence, and therefore treatment failure, was established at the onset of specifically defined diarrhea that had previously responded to antibiotic therapy and confirmed to be caused by *C. difficile* (3,9). The other two studies, McFarland et al (11) and Surawicz et al (10), involved patient populations who were recently prescribed antibiotics but showed no signs or symptoms of CDI. In these studies, clinical outcomes of diarrhea were recorded and *C. difficile* assays (positive culture, or the presence of toxin A or B) were performed on all patients. Further analyses were performed on patients with a positive *C. difficile* assay. All four studies used *S. boulardii* or placebo in combination with antibiotic therapy. Efficacy was reported as the prevention of diarrhea, and risks were described as adverse effects of treatment.

TABLE 1
Study descriptions

Author (reference)	Sample, n	Approximate mean age, years	Men, %	<i>Saccharomyces boulardii</i> dose	Duration	Antibiotics used
McFarland et al (3)	124 patients with active CDI (64 with an initial episode of CDI and 60 with a history of at least one previous CDI episode)	58.1	23	1 g/day or placebo	4 weeks	Not controlled
Surawicz et al (9)	168 (32 patients in high-dose vancomycin group)	61.8	26	2x250 mg capsules twice daily or placebo	Days 7 to 28 of antibiotic therapy	High-dose oral vancomycin (2 g/day) or low-dose (500 mg/day), or metronidazole (1 g/day), for 10 days
Surawicz et al (10)	180 (48 <i>Clostridium difficile</i> -positive)	47.8	68.9	2x250 mg capsules twice daily or placebo	Within 48 h of first antibiotic dose, and continued 2 weeks after last antibiotic dose	Not controlled
McFarland et al (11)	193	41	64.8	2x250 mg capsules twice daily	Within 72 h and continued 3 days after last antibiotic dose	Beta-lactam antibiotics (including medium to broad spectrum penicillins, combination penicillins, cephalosporins. Excluding penicillin G or V)

CDI *Clostridium difficile* infection**TABLE 2**
Prevention rates of recurrent *Clostridium difficile* infection

Author (reference)	Treatment, n (%)		P	Absolute risk reduction	OR*	OR (random) 95%CI*
	<i>Saccharomyces boulardii</i>	Placebo				
McFarland et al (3)	15 (26.3)	30 (44.8)	0.05	0.19	0.44	0.21–0.94
Surawicz et al (9)	39 (43.3)	37 (47.4)	–	0.04	0.85	0.46–1.56

*Calculated by Review Manager software (Cochrane Collaboration)

TABLE 3
Prevention rates of recurrent *Clostridium difficile* infection (CDI) in prespecified subgroups of patients

Author (reference)	Subgroups	Treatment, n (%)		P	Absolute risk reduction	OR*	OR (random) 95% CI*
		<i>Saccharomyces boulardii</i>	Placebo				
McFarland et al (3)	History of CDI	9 (34.6)	22 (64.7)	0.04	0.30	0.29	0.10–0.84
Surawicz et al (9)	High-dose vancomycin	3 (16.7)	7 (50)	0.05	0.33	0.20	0.04–1.01

*Calculated by Review Manager software (Cochrane Collaboration)

A total of 665 patients were included in all four trials. The mean age of subjects ranged from approximately 41 to 61.8 years and the proportion of male patients ranged from 23% to 68.9%. Baseline characteristics of the patients were significantly variable with differences in mean age, sex, treatment duration and control of concurrent antibiotics. Although all studies assessed rates of adverse events, only McFarland et al (3) reported adverse effects due to *S boulardii*.

Examining the prevention of CDI recurrence

McFarland et al (3) showed statistically significant differences in the efficacy of *S boulardii* in preventing recurrence within their patients, whereas Surawicz et al (9) did not (Table 2).

Each study also analyzed the data after population stratification. McFarland et al (3) divided their patients into subpopulations of individuals experiencing initial and recurrent CDI, and found a statistically significant reduction of relapses in the treatment group of patients with recurrent CDI (3). Surawicz et al (9) stratified their patients based on treatment antibiotic:

high-dose vancomycin, low-dose vancomycin or metronidazole (9). Data analysis demonstrated a trend toward reduction of CDI relapse in the treatment group of patients receiving high-dose vancomycin; however, it was not statistically significant (Table 3).

Prevention of CDI

Two trials, McFarland et al (11) and Surawicz et al (10), involved patients who were initiated on antibiotics without any form of diarrhea at baseline. These studies examined the prevention of AAD with subset population analyses on patients with positive *C difficile* toxin assays. In both studies, clinical symptoms of diarrhea and *C difficile* assays were measured independently in all patients; subjects were considered to be experiencing CDI if they had positive results for both. Further analyses were then performed for this subset population.

One study had a directionally negative outcome in the prevention of AAD, while the other showed statistically insignificant reductions in AAD (Table 4).

TABLE 4
Rates of failed primary prevention of *Clostridium difficile* infection

Author (reference)	Treatment, n (%)		Absolute risk reduction	OR*	OR (random) 95% CI*
	<i>Saccharomyces boulardii</i>	Placebo			
McFarland et al (11)	3 (3.1)	4 (4.2)	0.01	0.73	0.16–3.37
Surawicz et al (10)	3 (2.59)	5 (7.81)	0.05	0.31	0.07–1.36

*Calculated by Review Manager software (Cochrane Collaboration)

Risks

Side effects attributed to *S boulardii* included thirst, constipation and intestinal gas.

Of the two trials examining prevention of recurrence, McFarland et al (3) found a greater frequency of thirst and constipation in the *S boulardii* group than in the control group. Surawicz et al (9) showed no significant difference in the number of overall reported adverse events, nor was there a significant difference in the number of specific adverse events. Of the two trials investigating the prevention of AAD, adverse effect rates were not described for the group of patients who experienced CDI. Surawicz et al (10) reported no side effects in either the placebo or treatment groups. McFarland et al (11) found a higher rate of intestinal gas in the treatment group (n=7 [7.4%]) than in the control group (n=0; P=0.01) among patients who completed the adverse reaction forms (n=185 [96%]). Three of the four studies specified reasons for patient withdrawal; however, withdrawal rates between control and treatments groups were not compared (3,10,11). No studies compared the rate of withdrawal between the placebo and treatment groups.

Assessment of study quality

All studies included in the analysis were double-blind, randomized controlled trials. The studies used validated methods of detecting *C difficile*, and all had similar predefinitions of diarrhea, although none described validated methods of measuring stool consistency. Three studies had sufficient follow-up (3,9,11). In the literature, the mean time for recurrence is reported to be four weeks, which these studies met or exceeded (2). Surawicz et al (10) ambiguously stated that a subset of the population (23.3%) had follow-up for "several weeks after".

Not all studies conducted an intention-to-treat analysis. One study (9) exclusively provided the data from the stratified high-dose vancomycin group and failed to report the reason for withdrawals. Epidemiology of the patient population and enrollment data have been published elsewhere (12). All of the studies were sponsored by the manufacturer of *S boulardii*.

DISCUSSION

The rates of CDI development between the placebo and treatment groups were variable among the published studies investigating the prevention of CDI. The two studies that met the inclusion criteria for the present review reported a possible benefit in administering *S boulardii* in certain patient populations with recurrent CDI for secondary prevention without significant risk of adverse effects (3,9) (Table 3).

More research will be required before the use of *S boulardii* for primary prevention of CDI can be widely recommended. Generalizability of these studies to clinical practice is limited for a number of reasons: they excluded critically ill patients who may benefit from preventive therapy, and the mean age of

patients in the studies examining primary prevention was approximately 44 years, which is younger than the patient population usually affected by CDI (13).

Prevention of CDI recurrence

It is important to note the statistically significant difference between the groups at baseline in the McFarland et al (3) study; the patients in the placebo group had a mean number of 0.62 more surgeries in the previous year than the treatment group (P=0.02). Although the article did not specify the type of surgeries, abdominal surgery recently has been shown to increase the risk of CDI recurrence (2). In Surawicz et al (14), which analyzed patients based on a standardized antibiotic treatment, the population was not randomly assigned to the antibiotic therapy. Antibiotics were prescribed by the enrolling physicians based on the patients' previous exposure, tolerance to metronidazole and severity of disease. Therefore, patients in the high-dose vancomycin group were more severely ill patients who had underlying pseudomembranous colitis (14). The findings may not be extrapolated to all patients with CDI because the study reflected treatment in the most difficult to treat and severe cases of CDI.

It is unclear from these studies when to administer *S boulardii*. Effective treatment may consist of a combination of an antibiotic and *S boulardii*. This may ensure the clearance of *C difficile* at the end of the treatment and subsequent inactivation of the toxin receptor sites before allowing the germination and growth of spores in the colon (14). Two studies (3,9) differed in overlap periods between the treatment with the antibiotic and *S boulardii*. In one trial, the median overlap time between the study drug and the antibiotic was eight days, whereas in the other, it was four days.

Prevention of CDI

Two studies analyzed in the present review (10,11) focused primarily on general AAD, with subset population analyses on CDI. However, these lacked sufficient statistical power to allow for conclusions to be drawn about CDI. In addition, in Surawicz et al (10), there were disparate sample sizes in the treatment and the placebo group, which may have further confounded the results.

Limitations

One limitation of the present review is the exclusion of non-English studies. This may be significant because the use of probiotic therapy is much more prevalent in European countries where non-English studies are more likely to be published. In addition, the present report does not account for cost benefits and risks of *S boulardii* treatment, although another review (15) stated that *S boulardii* treatment is much more cost-effective than vancomycin after infection has occurred.

CONCLUSIONS

The present review of four trials suggests that there may be some benefit in using *S boulardii* for treatment and secondary prevention in patients experiencing recurrent CDI in conjunction with a particular concurrent antibiotic treatment. Because only a small number of studies address the primary prevention of CDI, more research is required before any changes in practice can be recommended with regard to using *S boulardii* prophylactically. The risks of administering *S boulardii* seem to be minimal compared with placebo, but because of case reports of potential morbidity secondary to serious fungemia, the use of this yeast agent should be considered on a case-by-case basis.

AUTHOR CONTRIBUTIONS: JMT performed the initial search, extracted the data and drafted the manuscript. LRD extracted the data, performed the statistical analysis and helped to draft the manuscript. CHL conceived the idea and helped to draft the manuscript. All authors read and approved the final manuscript.

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