The Role of *Saccharomyces boulardii* in the Treatment of Refractory Recurrent *Clostridium difficile* Infection

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**Abstract**

To review the literature surrounding the efficacy of *S. boulardii* for the treatment of recurrent *C. difficile* infections. Eligible articles included *S. boulardii* in patients with recurrent *C. difficile* infection. The primary endpoint examined was clinical resolution of infection with no further recurrences during follow-up. Results: Six studies met inclusion criteria. A case report showed resolution of recurrences in one patient, and an experimental trial showed a trend towards decreased recurrences in patients receiving *S. boulardii* (85% no further recurrences). Two randomized controlled trials found a significant decrease in recurrences for *S. boulardii* versus placebo (34.6% vs 64.7%, *P*=0.04; 16.7% vs 50%, *P*=0.05). One meta-analysis determined significant efficacy for *S. boulardii* in reducing relapses (RR 0.59, 95% CI 0.35-0.98), while another concluded there was insufficient evidence to recommend probiotics for *C. difficile* infection. *S. boulardii* may be considered adjunctively for patients with recurrent *C. difficile* infection who are refractory to antibiotic regimens alone.

1. Introduction

*Clostridium difficile* is a gram positive, spore-forming, anaerobic bacilli and the most frequent perpetrator of nosocomial infections affecting the gastrointestinal tract (Salliet, 2010; Segarra-Newnham, 2007). *Clostridium difficile* infections (CDI) are a major burden to the U.S. health system, accruing costs of about 3.2 billion dollars every year and is associated with a high rate of morbidity and mortality, resulting in possible bowel perforation, sepsis, or death (Surawicz, Brandt & Binion, 2013; Leong & Zelenitsky, 2013). Risk factors for the disease include recent antibiotic use, proton-pump inhibitors or other acid-suppressive therapies, advanced age, and immunosuppression.

Altered normal flora as a result of antibiotic treatment greatly increases risk of CDI, but paradoxically, antibiotics are also first-line therapy for treatment. Antibiotics are 80% effective for the first CDI episode; however as the gut microbiota becomes further disrupted, risk of CDI relapse rises. CDIs reoccur in approximately 20% of patients and multiple recurrences lead to an even greater risk of relapse at about 50-60% (Segarra-Newnham, 2007). Recurrences are thought to arise when spores surviving an antibiotic treatment course germinate and reiniterate disease in the absence of protective gut flora (Surawicz, Brandt & Binion, 2013).

A novel theory to combat recurrences uses colonization resistance by introducing healthy bacteria into the gut to restore the normal flora and prevent *C. difficile* from obtaining essential nutrients and surviving (Leong & Zelenitsky, 2013). This theory has led us to experimental treatments such as probiotics and fecal microbial transplant (FMT), in which feces of a healthy donor are implanted into the gastrointestinal tract of the diseased patient via oral, nasal, or rectal routes. Even patients who have had only a single CDI episode have markedly different bacterial flora and less bacterial diversity compared healthy individuals which demonstrates the great need to identify an effective therapy for restoring normal gut flora in these patients (Na & Kelly, 2011).

Probiotics are readily accessible to patients in stores and online, making them a mainstay of preventative therapy. Common products include single or multi-strain probiotic capsules, live culture probiotic beverages such as kombucha (fermented tea) or kefir, (fermented milk) as well as many food products like yogurts. Probiotics
provide benefits such as reinforcing the intestinal lining that acts as a barrier to invading organisms, enhancing the immune system, and increasing the growth and proliferation of the normal flora. (Surawicz, Brandt & Binion, 2013; Na & Kelly, 2011).

_Saccharomyces boulardii_ is a nonpathogenic yeast probiotic that has been studied in the treatment of recurrent CDI. _S. boulardii_ produces a protease that cleaves _C. difficile_'s toxins as well as their corresponding membrane receptors on the host intestinal cells (Castagliuolo, Riegler, Valenick, LaMont & Pothoulakis, 1999). By this mechanism, even after re-growth, _C. difficile_ cannot reinitiate disease because its toxins can no longer bind their receptors (Surawicz, et al. 2000). _S. boulardii_ grows at body temperature of 37°C and reaches a high steady-state concentration of 10^7 to 10^8 colony forming units in the colon in just a few days. The yeast is resistant to antibiotics, has a half-life of 2-5 days, and has been shown to clear the gastrointestinal tract after discontinuing use (McFarland, 2010). _S. boulardii_ is readily available inexpensively for 0.21 USD/capsule as a generic product, or under the trade name Florastor® (Biocodex, France) in the United States as lyophilized (freeze-dried) capsules, which are stable at room temperature for over a year. _S. boulardii_-containing probiotic capsules with their low cost, ease of use, and desirable administration may have a role for patients with recurrent CDI, defined as at least one prior episode previously treated with antibiotics.

In this literature review, relevant sources were identified through a literature search of PubMed (1962 to February 2016), Cochrane Library (1990 to 2015), _International Pharmaceutical Abstracts_ (2000 to 2015), and CINAHL (2001 to 2015) using the following keywords: _Clostridium difficile_, probiotic, recurrent, and _Saccharomyces boulardii._

Selection requirements included case reports, clinical studies, and meta-analyses utilizing _S. boulardii_-containing probiotics in the treatment of recurrent CDI as the primary outcome. Inclusion criteria were human data and studies published in English. Excluded studies comprised antibiotic-associated diarrhea as the primary outcome or treatment of recurrent CDI as a secondary outcome. One study was excluded because probiotic efficacy was determined by measuring the concentration of probiotic in stool samples, a practice determined to be clinically irrelevant (Elmer, McFarland, Surawicz, Danko & Greenberg, 1999; Pillai & Nelson, 2008). However, the complete outcome data were included in with a later study (Surawicz, 2000). Studies reviewed comprised one case report, one experimental trial, two randomized controlled trials, and two meta-analyses.

**Literature Review:**

1.1 Case Reports

A 1990 case report described a 67-year-old woman with multiple recurrences of CDI (Kimmey, Elmer, Surawicz, McFarland, 1990). Over the course of 38 weeks the woman experienced 8 episodes of recurrent CDI treated with multiple vancomycin tapers. Shortly after her eighth CDI episode, _S. boulardii_ was initiated, 250 mg capsules two by mouth twice daily, concurrently with a vancomycin taper. One week later, vancomycin was stopped and _S. boulardii_ was continued for 2 months and then tapered to one capsule twice daily for 10 days. Follow-ups at 10 and 18 months after discontinuing _S. boulardii_ determined that she experienced no further recurrences. While case report results have limited applicability to larger populations, this report demonstrates _S. boulardii_ as a potential adjunctive therapy for recurrent CDI.

1.2 Experimental Trials

Surawicz et al. performed an open trial in 1989 using _S. boulardii_ adjunctively to vancomycin in 13 patients with recurrent CDI (average of 3.6 recurrences). Patients were given a combination of vancomycin 250 mg orally four times daily for 10 days, plus _S. boulardii_ 2, 250 mg capsules twice daily started on day 5 of vancomycin treatment and continued for at least 30 days. The rationale for starting _S. boulardii_ after 5 days of vancomycin and continuing beyond antibiotic therapy was explained that _S. boulardii_ efficacy may be dependent on the ability of vancomycin to first clear _C. difficile_ from the GI tract, then allowing _S. boulardii_ to protectively colonize. Success was defined as no recurrence of diarrhea (3 or more loose stools per day for at least 2 consecutive days) for the duration of _S. boulardii_ treatment. Eleven of the thirteen patients (85%) reported no further recurrences within the 30 days of receiving _S. boulardii_, while two (15%) failed treatment. Both patients remained _C. difficile_ stool
culture positive following treatment, so it is possible that the vancomycin never cleared *C. difficile*, compared to the 11 successfully treated patients of which 82% were cytotoxin negative (P<0.001) following treatment. Seven patients were contacted (range 2-150 days, median 6 days) after cessation of *S. boulardii* and reported no further recurrences. This study’s limitations included small patient population, lack of a control group or randomization to antibiotic groups, and the follow-up may not have been long enough to detect delayed recurrences.

1.3 Randomized Controlled Trials

A double-blind randomized placebo-controlled trial utilized *S. boulardii* in combination with antibiotics for 64 patients with an initial episode of CDI and 60 with a recurrence (McFarland et al., 1999a). Patients received metronidazole or vancomycin (chosen by the physician) in combination with either placebo or *S. boulardii* (two 250 mg capsules twice daily) started within 4 days of antibiotics and continued for 4 weeks with an additional 4-week follow-up. Study drug failures were defined as presence of diarrhea, pseudomembranes, or a positive *C. difficile* assay. Of the 124 patients, 30 of 67 (44.8%) failed treatment on placebo whereas 15 of 57 (26.3%) failed treatment on *S. boulardii* (P=0.05). Multivariate analysis was performed and *S. boulardii* was shown to be significant in reducing recurrences in patients with a history of recurrences, (34.6% vs 64.7%, P=0.04) but not in patients presenting with their first CDI episode (19.3% vs 24.2%, P=0.86). Adverse reactions reported with *S. boulardii* were increased thirst (9%) and constipation (14%). This study suggests that *S. boulardii* may be useful following multiple CDI recurrences when the gut flora has been markedly altered. Limitations include that patients were not randomized to antibiotic groups and this study was underpowered to detect a significant difference in patients presenting with their first episode.

An add-on study to the previous attempted to control for the dose and duration of antibiotics in combination with *S. boulardii* in hopes of defining a specific regimen for the treatment of recurrent CDI (McFarland et al., 1999b). The study extracted results from a different trial, which randomized patients to three antibiotic groups: metronidazole (1 g/day), low-dose vancomycin (500 mg/day), and high-dose vancomycin (2 g/day), plus *S. boulardii*. Both the metronidazole and low-dose vancomycin groups were found to be nonsignificant in reducing recurrences compared to placebo, and therefore this sub-study focused only on patients prescribed high-dose vancomycin. Patients were prescribed a 10-day course of high-dose vancomycin (2 g/day) plus placebo or *S. boulardii* two 250 mg capsules twice daily started on day 7 of vancomycin treatment and continued for 28 days. Study duration was 8 weeks with an additional 5-month follow-up. Of the 168 patients, only 32 were prescribed high-dose vancomycin due to more severe infection and all had a history of at least one or more prior episode of CDI within the past year. Drug failures were defined as presentation of diarrhea after discontinuation of antibiotics and before the end of the 8-week study duration. Of the patients on high-dose vancomycin, 3 of 18 (16.7%) taking *S. boulardii* experienced a relapse compared with 7 of 14 (50%) taking placebo (P=0.05). Four patients receiving placebo also experienced two relapses during the trial. During the 5-month follow-up, 29 patients were successfully contacted and 3 of 13 (23%) receiving placebo had recurred compared to zero patients taking *S. boulardii*. No adverse reactions were reported.

Metronidazole and low-dose vancomycin were ineffective in the parent study possibly because *C. difficile* was not completely cleared. In these groups, 41% of metronidazole patients and 11% of low-dose vancomycin patients remained *C. difficile* positive following antibiotic treatment, versus 100% clearance in the high-dose vancomycin group. It is also important to note that the 1000 mg/day dose of metronidazole may have been subtherapeutic. The Infectious Diseases Society of America recommends 1500 mg daily (Cohen, Gerding & Johnson, 2010). A limitation of this study was the small number of patients receiving high-dose vancomycin due to randomization based on disease severity. As these patients presented with more severe disease, they may be inherently different from the other two antibiotic groups. The results may only be applicable to this specific patient population.

1.4 Meta-analyses

In a meta-analysis in 2006 of probiotics for prevention of antibiotic associated diarrhea and treatment of CDI, McFarland et al. evaluated 6 randomized controlled trials (354 patients) for CDI and 25 (2,810 patients) for
antibiotic associated diarrhea. Of the 6 CDI studies, 2 using *S. boulardii* reported a significant effect of

**Table 1: Summary of Studies Evaluating *S. boulardii* for the Treatment of Recurrent CDI**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Patients</th>
<th>Treatment/Duration</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kimmey (1990)</td>
<td>Case Report</td>
<td>n=1</td>
<td><em>S. boulardii</em>: 2x250 mg caps twice daily x 2 months – then tapered to 1 capsule twice daily x 10 days</td>
<td>10, 18 months</td>
<td>No recurrences</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Antibiotics: vancomycin taper (dose not specified) x 1 week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surawicz (1989)</td>
<td>Experimental Trial</td>
<td>n=13</td>
<td><em>S. boulardii</em>: 2x250 mg caps twice daily started on day 5 of vancomycin, continued for 30 days</td>
<td>30 days</td>
<td>11/13 (85%) reported no recurrences</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Antibiotics: vancomycin 250 mg four times daily x 10 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McFarland (1994)</td>
<td>Randomized</td>
<td>n=124</td>
<td><em>S. boulardii</em>: 2x250 mg caps twice daily started within 4 days of antibiotics x 4 weeks or placebo</td>
<td>4 weeks</td>
<td><em>S. boulardii</em> in initial episode: (19.3% vs 24.2%, P=0.86)</td>
</tr>
<tr>
<td></td>
<td>Controlled Trial</td>
<td>(64 pts with an initial episode, 60 with a recurrence)</td>
<td>Antibiotics: metronidazole or vancomycin according to prescriber discretion (dose, duration not specified)</td>
<td></td>
<td><em>S. boulardii</em> in history of recurrences: (34.6% vs 64.7%, P=0.04)</td>
</tr>
<tr>
<td>Surawicz (2000)</td>
<td>Randomized</td>
<td>n=168</td>
<td><em>S. boulardii</em>: 2x250 mg caps twice daily started on day 7 of vancomycin x 28 days or placebo</td>
<td>8 weeks</td>
<td><em>S. boulardii</em> plus high-dose vancomycin: 3/18 (16.7%) relapsed vs 7/14 (50%) taking placebo (P=0.05)</td>
</tr>
<tr>
<td></td>
<td>Controlled Trial</td>
<td>(32 in high-dose vancomycin group)</td>
<td>Antibiotics: metronidazole (1 g/day), low-dose vancomycin (500 mg/day), or high-dose vancomycin (2 g/day) x 10 days</td>
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</table>
probiotics versus placebo in reducing the incidence of recurrent CDI, while 4 studies using non-S. boulardii probiotics determined there was no difference. Both studies showing significance are discussed above and of note, these two studies and this meta-analysis were written by the same author. Combined efficacy for the 6 studies showed that probiotics are significantly effective for decreasing risk of CDI recurrences (RR for CDI 0.59 [95% CI 0.41-0.85] P=0.005). S. boulardii was the only probiotic strain that exhibited significant efficacy for reducing recurrences. Adverse effects reported were thirst and constipation with S. boulardii and no cases of fungemia, bacteremia, or other serious events were reported in the 31 trials and over 3,000 patients included. The authors concluded that probiotics are effective for the treatment of CDI.

Conversely, a Cochrane review determined that there is insufficient evidence to recommend probiotics as an adjunct to antibiotics for the treatment of CDI (Pillai & Nelson, 2008). Four randomized controlled trials of probiotics in combination with antibiotics were evaluated, two of which are discussed above, while the other two used probiotics other than S. boulardii (Surawicz, 2000; McFarland, 1994; Wullt, Haglslatt, Odenholt, 2003; Lawrence, Korzenik, Mudy, 2005). The authors determined clinical heterogeneity among studies in terms of antibiotic use and defining recurrent CDI were such that no current recommendation can be made. The authors also stated that the trials analyzed were likely too small and lacked the power to detect a significant difference.

**Discussion:**

The 2013 American College of Gastroenterology guidelines for CDI conclude there is only weak evidence for S. boulardii in recurrent CDI, but fecal microbiota transplant (FMT) may be considered after a third recurrence and failure of a pulsed vancomycin regimen. The 2010 SHEA/IDSA guidelines for CDI reference the McFarland et al. clinical trial stating that S. boulardii in combination with vancomycin appears to decrease recurrences. However, they expressed about possible fungemia in immunocompromised patients (Cohen, Gerding, Johnson, 2010). The authors conclude that there is no compelling evidence for probiotics in the treatment of CDI recurrences.

Although S. boulardii is traditionally safe and nonpathogenic, probiotics are not completely benign and the possibility of fungemia exists. Some major risk factors for bloodstream infections include severe immunosuppression and prematurity in infants, while minor risk factors include presence of a central venous catheter, an impaired intestinal barrier (diarrhea or inflammation), concomitant administration of a broad-spectrum antibiotic that does not cover the probiotic, and administration of the probiotic via a J-tube. Despite this, overall risk of bacteremia or fungemia from probiotic organisms is extremely low (< 1/1,000,000).
and there is no evidence that risk of infection from a probiotic is any greater than risk from a commensal organism (Hedge, Strain, Heins, Farver, 2008). Additionally, it is believed that bloodstream infection from one of these organisms is a marker of extremely bad health and poor prognosis. In general, the above studies in patients cited to be at increased risk of fungemia demonstrate only minor adverse reactions associated with _S. boulardii_ and no serious adverse events were reported, although it is important to note that most excluded severely immunocompromised patients.

**Conclusion:**

Efficacy data for _S. boulardii_ in recurrent CDI were limited and the studies analyzed used small patient populations with varying follow-up, which may have concealed further recurrences. Durations of antibiotics and probiotics among studies also varied making a precise recommendation on when and how to use _S. boulardii_ in recurrent CDI difficult.

Nonetheless, the studies examined generally showed benefit in patients taking the probiotic with minimal risk, demonstrating that it might be a reasonable option to consider in some patients. _S. boulardii_ may be of benefit in patients who have suffered from multiple recurrences, having exhausted antibiotic avenues such as taperers, and are aesthetically or financially hesitant to undergo invasive FMT, as this is currently the only guideline-recommended option. If a patient is willing to attempt a trial of _S. boulardii_ and is unsuccessful resulting in subsequent recurrences, FMT should be strongly considered. In those with severe immunosuppression or a central venous catheter, probiotics should be used cautiously or alternative treatment should be selected.

_S. boulardii_ is readily available, inexpensive, desirable to consumers, and poses little risk in individuals without severe immunosuppression. Due to the wide array of probiotic products available on the market, products with regulatory quality control programs should be selected if possible. As an adjunct treatment to antibiotics, _S. boulardii_ may be an affordable and accessible option for trial in patients with recurrent CDI, refractory to multiple antibiotic regimens, before resorting to undergo invasive FMT.

7. **References**


