Prevention of Clostridium difficile infection with Saccharomyces boulardii: a systematic review

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CRD summary
The review found that Saccharomyces boulardii was well tolerated and significantly reduced recurrent antibiotic-associated diarrhoea caused by Clostridium difficile infection, particularly with concurrent high-dose vancomycin. Its effect on primary prevention was not significant. In view of limitations that arose from the review process and the evidence provided, the extent to which the authors' conclusions are reliable is unclear.

Authors' objectives
To evaluate the effectiveness and safety of Saccharomyces boulardii in the prevention of primary and recurrent Clostridium difficile infection.

Searching
MEDLINE from August 1966 to January 2004, EMBASE from 1980 to 2004 (week 36), CINAHL from 1982 to August 2004 (week 4) and The Cochrane Library were searched for publications in English; search terms were reported. Bibliographies of each retrieved article and relevant reviews were handsearched. Manufacturers of S. boulardii probiotics were contacted for relevant references.

Study selection
Randomised controlled trials (RCTs) that evaluated the effectiveness of S. boulardii in adult patients for prevention of primary or recurring C. difficile infection were eligible for inclusion. Trials were excluded if they did not examine clinical endpoints such as onset of diarrhoea or did not directly test for the presence of C. difficile either by microbiological culture or detection of toxins A or B. Review articles were excluded. Eligible outcomes were benefit (defined as a reduction in C. difficile-associated diarrhoea) and risk (defined as the adverse effects of S. boulardii treatment). Studies were excluded if S. boulardii was used for other indications or the intervention included use of other probiotics or drugs. Most of the included studies used a twice daily dosage of 250mg capsules of S. boulardii (one study used 1g/day) versus placebo. For studies of C. difficile recurrence, S. boulardii treatment duration was three to four weeks. For studies of C. difficile prevention, treatment commenced within two to three days of first antibiotic dose and continued until three days to weeks after the last antibiotic dose. There were significant differences between studies in treatment duration and control of current antibiotics (low-dose or high-dose vancomycin, metronidazole or beta-lactam antibiotics and medium to broad spectrum penicillins, combination penicillins or cephalosporins). Mean age of patients ranged from 41 to 61.8 years. The proportion of males ranged from 23% to 68.9%. Only one study reported adverse effects specifically due to S. boulardii.

One reviewer performed the study selection.

Assessment of study quality
No formal validity assessment was made, but the reviewers assessed some relevant criteria (study design, duration of follow-up, intention-to-treat analysis and use of validated methods).

The authors did not state how many reviewers performed the validity assessment.

Data extraction
The number of events for each outcome was extracted in order to calculate absolute risk reduction (RR) and odds ratios (OR), with 95% confidence intervals (CI).

Two reviewers performed data extraction using a structured chart.
Methods of synthesis
Studies were divided into two groups based on their examination of primary or secondary prevention of \textit{C. difficile} infection. Subgroup analyses were reported for individual studies. A narrative synthesis was provided.

Results of the review
Four relevant RCTs were identified (n=665, range 124 to 193). All studies were double-blind, used validated methods for detecting \textit{C. difficile} and had similar predefinitions of diarrhoea (although none described validated methods of measuring stool consistency). Three studies had sufficient follow-up and three studies performed an intention-to-treat analysis. All four RCTs reported withdrawal rates, but none compared these rates in the treatment and placebo groups.

\textbf{Prevention of \textit{C. difficile} recurrence (two RCTs):} One RCT reported that \textit{S. boulardii} significantly reduced recurrence of infection (RR 0.19 and OR 0.44, 95\% CI 0.21 to 0.94) and one RCT found no significant effect.

One study performed subgroup analyses for the different antibiotics used, none of which was significant. But there was a trend towards reduction in \textit{C. difficile} infection relapse in the recurrent treatment group of patients who received high-dose vancomycin in addition to \textit{S. boulardii} (RR 0.33 and OR 0.20, 95\% CI 0.04 to 1.01). The other study performed a subgroup analysis for patients with a history of recurrent \textit{C. difficile} infection and found that \textit{S. boulardii} significantly reduced the recurrence of infection (RR 0.30 and OR 0.29, 95\% CI 0.10 to 0.84).

\textbf{Adverse events:} One RCT reported that there were no significant differences between intervention and control groups for overall adverse events and those related specifically to \textit{S. boulardii} treatment. The other RCT reported greater frequency of thirst and constipation in the \textit{S. boulardii} group compared to controls (significance not reported).

\textbf{Prevention of \textit{C. difficile} infection (two RCTs):} Both studies performed subgroup analyses for patients with \textit{C. difficile} infection if they had both clinical symptoms of diarrhoea and positive \textit{C. difficile} toxin assays. Neither study found \textit{S. boulardii} had a significant effect on reducing antibiotic-associated diarrhoea caused by \textit{C. difficile} infection.

\textbf{Adverse events:} One RCT reported no side effects in either the placebo or treatment group. The other RCT found a statistically significantly higher level of intestinal gas in the \textit{S. boulardii} group (7.4\%) than in the placebo group (0\%) among the 96\% of patients who completed the adverse reaction forms.

Authors' conclusions
\textit{S. boulardii} appeared 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 was poorly defined and more research was required before changes in practice were recommended.

CRD commentary
The review addressed a well-defined question in terms of study design, but the authors did not clearly define relevant interventions with respect to concurrent antibiotic intake. There also seemed to be inconsistencies related to the definition of \textit{C. difficile} infection and whether adverse events were or were not related to the use of \textit{S. boulardii}. Relevant databases were searched, but only for studies published in English and so some relevant studies may have been missed. Relevant data were provided related to study quality. No efforts were reported to reduce error and bias in study selection, validity assessment and data extraction (except two reviewers performed data extraction). Relevant study details were reported, but specific overall duration of treatment was not reported for studies of prevention of infection and no details were reported for loss to follow-up. No data was reported relevant to the placebos used. A narrative synthesis was provided due to heterogeneity and the low numbers of studies. The results of subgroup analyses were reported for studies of prevention, but no reason was given for not providing overall results. The abstract reported a risk reduction of 0.53 for reduction in relapses in patients who experienced recurrent \textit{C. difficile} infection in one study, but the figure given in Table 2 was 0.19. Some conclusions were based on very low numbers, particularly those for adverse events. In view of limitations that arose from the review process and the limited evidence provided, the extent to which the authors’ conclusions are reliable is unclear.

Implications of the review for practice and research
\textbf{Practice:} The authors stated that the results of these studies may not be applied generally to clinical practice as they
excluded critically ill patients who might benefit from preventative therapy and the mean age of the patients (44 years) in the studies of primary prevention was younger than in the usual patient population affected by *C. difficile* infection.

**Research:** The authors stated that more research was required before use of *S. boulardii* could be widely recommended for the primary prevention of *C. difficile* infection.

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