Probiotics and *Clostridium difficile*-associated diarrhoea

**Introduction**

*Clostridium difficile* is now recognised as the major cause of hospital acquired infectious diarrhoea.

Data from Sir Charles Gairdner Hospital (SCGH) in Perth, Western Australia, is typical of many similar hospitals in developed countries. SCGH is a 600 bed adult university teaching hospital. During the period 1983 to 1992, *C. difficile* was detected in 917 patients who were being investigated for diarrhoeal illness. Up to 120 patients a year were infected, most of these being elderly females. Incidence rates increased from 23/100,000 occupied bed days in 1983 to 56/100,000 occupied bed days in 1990.

Two factors appeared particularly important in the rapid rise of infection with *C. difficile*. Firstly, increased and inappropriate use of certain broad-spectrum antibiotics predisposed more patients to infection and, secondly, contamination of the hospital environment with *C. difficile* was a significant problem.

The increasing incidence of *C. difficile*-associated diarrhoea (CDAD) presents important economic implications for health care systems. One is that patients with CDAD tend to spend longer in hospital, resulting in significant costs to the health care system. Much of this increased length of hospital stay is because of apparent relapses in CDAD (thought to be about 20% of cases) following therapy with either vancomycin or metronidazole. Most of these apparent relapses are actually reinfections with a different strain of *C. difficile*. Thus prevention of infection or re-infection with *C. difficile* is an important problem and alternatives to conventional antibiotics have been sought.

Probiotics have been suggested for the treatment of infectious gastroenteritis in general, and specifically for the treatment and prevention of CDAD. The mechanisms of action of probiotics have been summarised by Filho-Lima et al. Four possibilities exist:

- Antagonism through production of inhibitory substances.
- Competition with the pathogen for adhesion sites or nutrients.
- Immunomodulation of the host.
- Inhibition of toxins.

Two probiotics have been used for CDAD, *Saccharomyces boulardii* and *Lactobacillus GG*.

**Saccharomyces boulardii**

*S. boulardii* is a non-pathogenic yeast which is either closely related to or the same as *S. cerevisiae*, which is widely used in the baking and brewing industries. Consumed orally, *S. boulardii* reaches around 10^8 per gram of stool soon after initiating therapy (1g/day), is rapidly cleared and no longer detectable three to six days following cessation of therapy.

Studies in hamsters during the 1980s indicated that *S. boulardii* was beneficial for pseudomembranous colitis due to overgrowth of toxigenic *Clostridium difficile*. In an early trial, diarrhoea was resolved in 85% of treated patients, although the numbers of patients was low.

A subsequent double-blind, randomised, placebo-controlled study evaluated the efficacy of *S. boulardii* administered to adults with either acute initial (n=64) or recurrent (n=60) attacks of CDAD. Patients received a standard course of vancomycin or metronidazole with either *S. boulardii* (500 mg bd) or placebo for four weeks and were followed for four weeks after completing treatment. The recurrent CDAD group treated with *S. boulardii* had significantly fewer relapses (35%) compared with the placebo group (65%); however, no benefit was seen in patients with primary CDAD. Thus *S. boulardii* therapy should be reserved for patients with recurrent disease.

Although our experiences with *S. boulardii* are limited, they have been successful. So far 25 elderly patients with recurrent CDAD have been treated with vancomycin plus *S. boulardii* (500 mg bd) for a week, followed by another 3 weeks of just *S. boulardii*. Twenty three of the 25 patients responded with one patient being lost to follow up [Golledge and Riley, unpublished].

The efficacy of *S. boulardii* in preventing recurrence of CDAD may depend on concentrations of the organism achieved in stools. In a recent study, patients with recurrent CDAD received a 10 day course of antibiotics together with a 28 day course of either *S. boulardii* or placebo. Patients with recurrences had significantly
lower concentrations of S. boulardii in their stools than patients who did not have recurrences (2.5 x 10^4 cfu/g versus 1 x 10^3 cfu/g). The mechanism of action of S. boulardii appears to be through the production of a protease that inactivates C. difficile toxins.

**Lactobacillus GG**

Lactobacillus GG is now classified as a strain of *L. rhamnosus*. It is resistant to acid and bile degradation, and adheres tightly to human intestinal cells, thereby allowing it to colonise the bowel more successfully than other strains of Lactobacillus. This strain also elaborates an antimicrobial substance that inhibits several bacteria including C. difficile. A single administration of Lactobacillus GG results in colonisation of the gastrointestinal tract for one to three days in the majority of treated individuals and for up to seven days in 30% of treated patients.

Several papers from the same group have reported the use of Lactobacillus GG in children and in adults with recurrent CDAD. In the largest study to date, 27 of 32 treated patients (84%) had no further recurrences. Five patients relapsed, of whom three responded successfully to a second course of treatment. In the second study, over 650 hospital patients taking antibiotics were randomised to receive either yoghurt or no yoghurt while on therapy. Although the sample size was small, those taking yoghurt had a significantly reduced incidence of diarrhoea and CDAD (Table 1). Over a three month period there was a 50% reduction in both the incidence of symptomatic diarrhoea and CDAD [Golledge and Riley, unpublished].

**Conclusions**

With the incidence of CDAD continuing to rise around the world and the significant economic impact this is having, additional therapies are required. Non-antibiotic approaches offer several advantages, not the least of which is a reduction in vancomycin use. These forms of treatment still require further evaluation; however, they offer promise for the eventual control of recurrent infection.

**References**


**Table 1.** Diarrhoea and CDAD following clindamycin therapy with or without yoghurt [Golledge and Riley, unpublished data].

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<tr>
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<th>Diarrhoea</th>
<th>No diarrhoea</th>
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<tr>
<td>Yoghurt</td>
<td>1 (No C. difficile)</td>
<td>15</td>
</tr>
<tr>
<td>No yoghurt</td>
<td>7 (2 C. difficile)</td>
<td>10</td>
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Fisher’s exact test, p=0.02