There’s strength in numbers . . .

Probiotic Therapy for *C. difficile*?

By Jay Hardy, CLS, SM (NRCM)

*Clostridium difficile* associated disease (CDAD) continues to be an increasing burden to the health care system, totaling more than $1 billion per year in the United States.

**Symptoms and Traditional Treatment**

Symptoms of colitis and diarrhea associated with CDAD often first present during or shortly after a course of antibiotic therapy. Treatment of patients with *C difficile* infection with oral metronidazole or vancomycin reduces morbidity and mortality, although the number of patients that do not respond to metronidazole is increasing.

Another cause for alarm is that, despite initial response rates of greater than 90%, 15-30% of patients have a relapse in symptoms after successful initial therapy, usually in the first few weeks after treatment is discontinued.

**Super strains**

During the past five years, the virulence of this organism has increased. Recently it has reached epidemic proportions in some hospital settings, prompting Medicare to propose adding CDAD to the list of hospital-acquired conditions for which reimbursements may be cut.

![Clostridium difficile](image1.png)

**Figure 1:** *C. difficile* is a gram positive, spore forming, anaerobic, rod shaped bacteria.

In May of 2010, the more virulent NAP1 strain of *C. difficile* appeared in Phoenix, Arizona, where ten patients became severely ill, two of which have died. The NAP1 strain is known to produce up to 20 times as much toxin as other

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To ensure rapid and reliable turn around time, Hardy Diagnostics maintains six distribution centers, and produces over 3,000 products used in clinical and industrial microbiology laboratories throughout the world.
strains and has been officially identified in 39 states.

Thus, it is imperative that new effective preventive and therapeutic strategies be implemented in hospitals to decrease the rate of CDAD infections.

Figure 2: Cross section of diseased colon tissue showing the eruption of epithelial cells and the development of a pseudomembrane due to C. difficile infection.

Probiotics – A Better Way?

Years ago, the use of probiotics had been suggested as a way to prevent and possibly cure CDAD. Probiotics are living or lyophilized organisms used to re-populate the intestinal tract with normal healthy flora. Among the species that have been studied and found to be successful are:

- **Saccharomyces boulardii**
- **Bifidobacterium spp**
- **Lactobacillus ramosus**
- **Lactobacillus acidophilus**
- **Lactobacillus plantarum**
- **Lactobacillus casei**

These organisms must be capable of surviving the low pH of the stomach and duodenum, resist the effect of bile acids in the upper small intestine when ingested, and temporarily colonize the gastrointestinal tract by binding to the intestinal and colonic mucosa.

Probiotics exert their beneficial effects through various mechanisms, including lowering intestinal pH, decreasing colonization and invasion by pathogenic organisms, and modifying the host immune response. Probiotic benefits associated with one species or strain do not necessarily hold true for others.

Probiotics have been used not only for CDAD, but for other causes of antibiotic-associated diarrhea, travelers' diarrhea, rotavirus, irritable bowel syndrome, ulcerative colitis, Crohn's disease, and vulvovaginal candidiasis.

Generally considered safe and well tolerated, probiotics cause only occasional side effects of bloating and flatulence. They should be used cautiously in patients who are critically ill or severely immuno-compromised or those with central venous catheters since systemic infections may rarely occur.

Probiotic administration thus may not be appropriate for ICU patients, due to the chance of septicemia. Bacteria-derived probiotics should be separated from antibiotics by at least two hours.

Probiotic and CDAD Studies

Let’s take a look at some of the studies completed during the last two years.

The British Nutrition Foundation states in March of 2010, “There is good evidence that probiotics are effective in preventing antibiotic-associated diarrhoea and, although only few studies have been carried out so far, probiotic microorganisms also seem to have the potential to prevent the potentially fatal *Clostridium difficile*-associated diarrhoea.”

At the University of Wisconsin, researchers found promising results using the commercial product Florajen. These capsules contain only *Lactobacillus acidophilus*. The manufacturer claims counts of 20 billion CFUs per capsule. In the placebo group of this study, 37% of elderly patients on antibiotics developed antibiotic-associated diarrhea. With the Florajen group, only 17% developed the disease.
A review of studies by researchers at St. Josephs Healthcare in Ontario, Canada concluded that “Saccharomyces boulardii seems to be well tolerated and may be effective for secondary prevention in some specific patient populations with particular concurrent antibiotic treatment.”

Researchers in Tempe, Arizona, report pilot data that is strongly suggestive that bifidobacteria and lactobacilli combinations may be effective in preventing this hospital-acquired infection and possibly reducing severity when diagnosed.

A Puget Sound VA Healthcare System study concludes, “Overall, probiotics offer a promising strategy for the prevention and treatment for AAD (antibiotic associated diarrhea) and CDI (Clostridium difficile infection).”

A study in Sweden in 2010, found that when patients that were being treated with antibiotics were given fruit juice spiked with Lactobacillus plantarum, the overall risk of developing loose or watery stools was significantly lower as was the occurrence of nausea. However, patients with severe diarrhea were unaffected.

St. Louis University School of Medicine researchers polled gastroenterologists and other physicians and found that “All physicians responded that they believed probiotics to be safe for most patients and 98% responded that probiotics have a role in treating gastrointestinal illnesses or symptoms.” Even though a belief in the effectiveness of probiotics exists, this does not always result in prescribed treatment by the physician.

In a small study in Duluth, Minnesota, eight patients, each of whom experienced recurrent episodes of CDAD, were treated with metronidazole or vancomycin combined with daily intake of kefir, an over-the-counter liquid probiotic dairy product. All eight patients successfully resolved their infections and ceased to experience any further diarrhea.

Not all studies have supported the use of probiotics. Many of these studies suffer from a lack of standardization and quality control of the probiotics being tested. Reviewers complain of a lack of consistent study design, probiotic dose, strain, and duration of therapy. To be effective, the proper strain and an adequate dose must be used and verified.

The Gao Study in China

Perhaps the most impressive study to date has been the Gao study in China that was published in the American Journal of Gastroenterology in February of 2010. In this randomized, double-blind, placebo-controlled study, 255 patients were tracked for 21 days following antibiotic therapy. Within 36 hours of being treated they were given either one or two capsules containing a mixture of L. acidophilus and L. casei, each containing a total of 50 billion CFUs. This probiotic therapy continued for five days after the last antibiotic dose. With the administration of two probiotic capsules daily, only 1.2% of the patients acquired CDAD, opposed to 23.8% of the patients in the placebo group. See the chart below.

Gao concluded that “The proprietary probiotic blend used in this study was well tolerated and effective for reducing the risk of Antibiotic-associated Diarrhea (AAD) and, in particular, CDAD in hospitalized patients on antibiotics. A dose-ranging

<table>
<thead>
<tr>
<th>Patients showing AAD symptoms</th>
<th>Duration of symptoms</th>
<th>CDAD confirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>44.1%</td>
<td>6.4 days</td>
</tr>
<tr>
<td>One probiotic capsule daily</td>
<td>28.2%</td>
<td>4.1 days</td>
</tr>
<tr>
<td>Two probiotic capsules daily</td>
<td>15.5%</td>
<td>2.8 days</td>
</tr>
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effect was shown with 100 billion CFU yielding superior outcomes and fewer gastrointestinal events compared to 50 billion CFU.”

The use of probiotics in this study represents a 95% reduction in the incidence of CDAD. This study clearly demonstrates that there is indeed “strength in numbers” in that successful patient outcomes were dose dependent requiring a treatment regimen of 100 billion CFUs per day.

This well controlled study shows conclusive results that should encourage the use of probiotics in patients receiving antibiotic therapy. Again, previous studies may have produced disappointing results due to an inadequate dose or the use of ineffective strains of probiotics.

In March of 2010, further evidence of the efficacy of probiotics was provided by a group of microbiologists in Argentina who found that when toxin producing C. difficile was cultured in the presence of bifidobacteria and lactobacilli, the amount of toxin A and B was decreased significantly compared to pure cultures of C. difficile.

**Alternative Therapy – Fecal Transplants**

As revolting as it may seem, for the treatment of stubborn recurring CDAD, fecal transplants have been attempted in the past. In the literature, more than 150 patients have received feces from a healthy donor, either infused through an enema, or through a nasoduodenal or nasogastric tube.

**Alternative Therapy – Non-toxigenic C. difficile**

Another innovative approach is to administer non-toxigenic strains of Clostridium difficile, which have been found to be highly effective in preventing toxigenic C. difficile infection in hamsters when given following a single dose of an antimicrobial agent.

**Conclusion**

When given in adequate doses and with the appropriate strains, probiotics have been shown to effectively prevent or provide therapy for Clostridium difficile associated disease (CDAD); demonstrating a simple case of the “good guys crowding out the bad guys.”

Probiotics are not patented and are thus inexpensive, which is why they will never be mass marketed by the major pharmaceutical firms.

Once again, the simple, natural, and non-invasive treatments sometimes prove to be the most effective.

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